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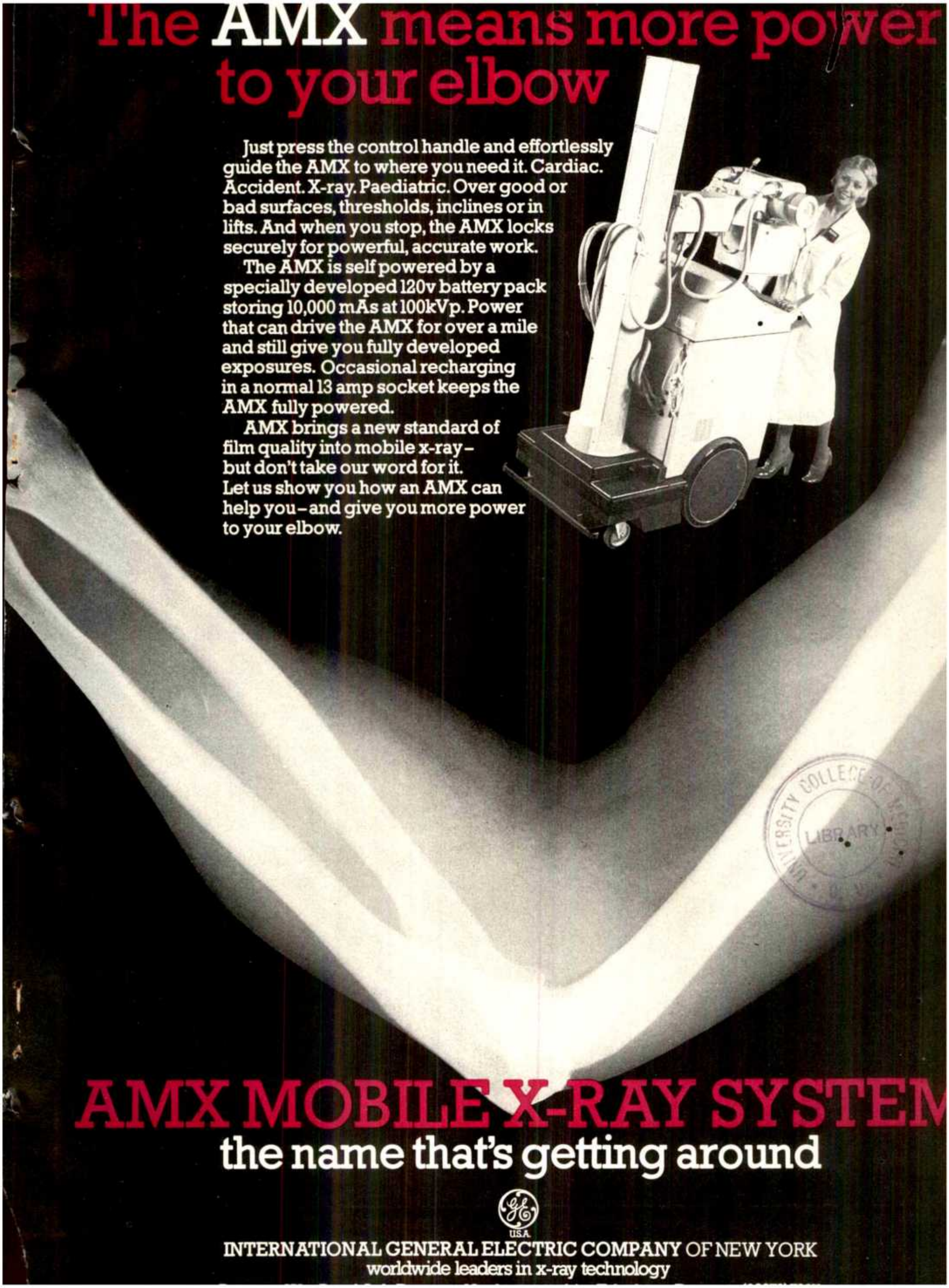

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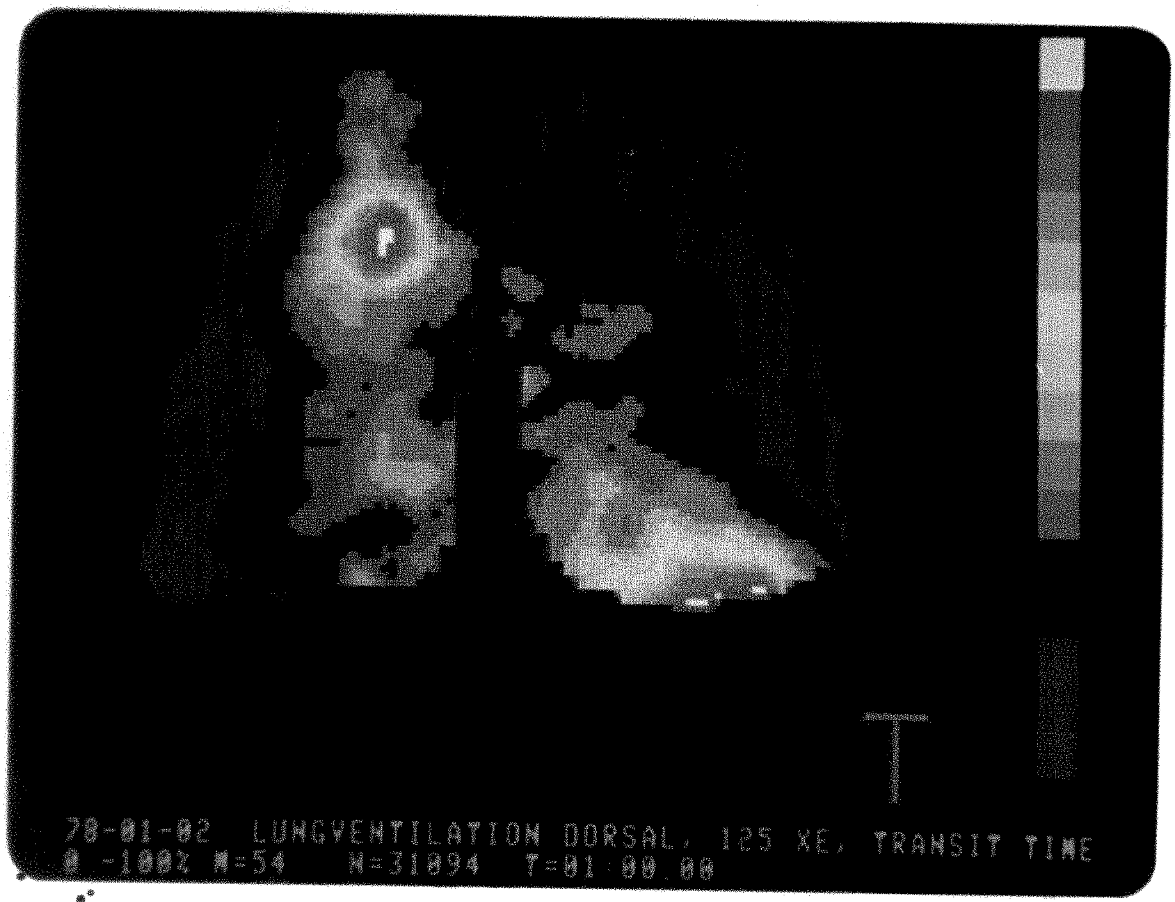
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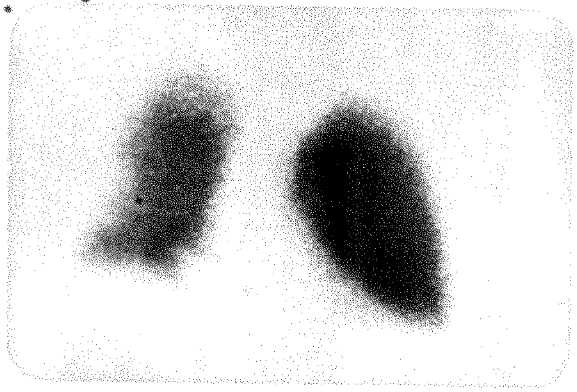

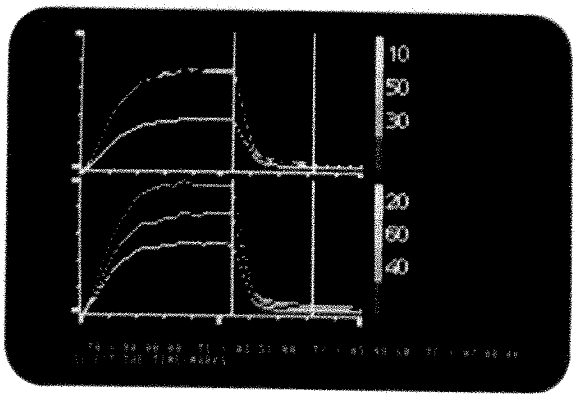

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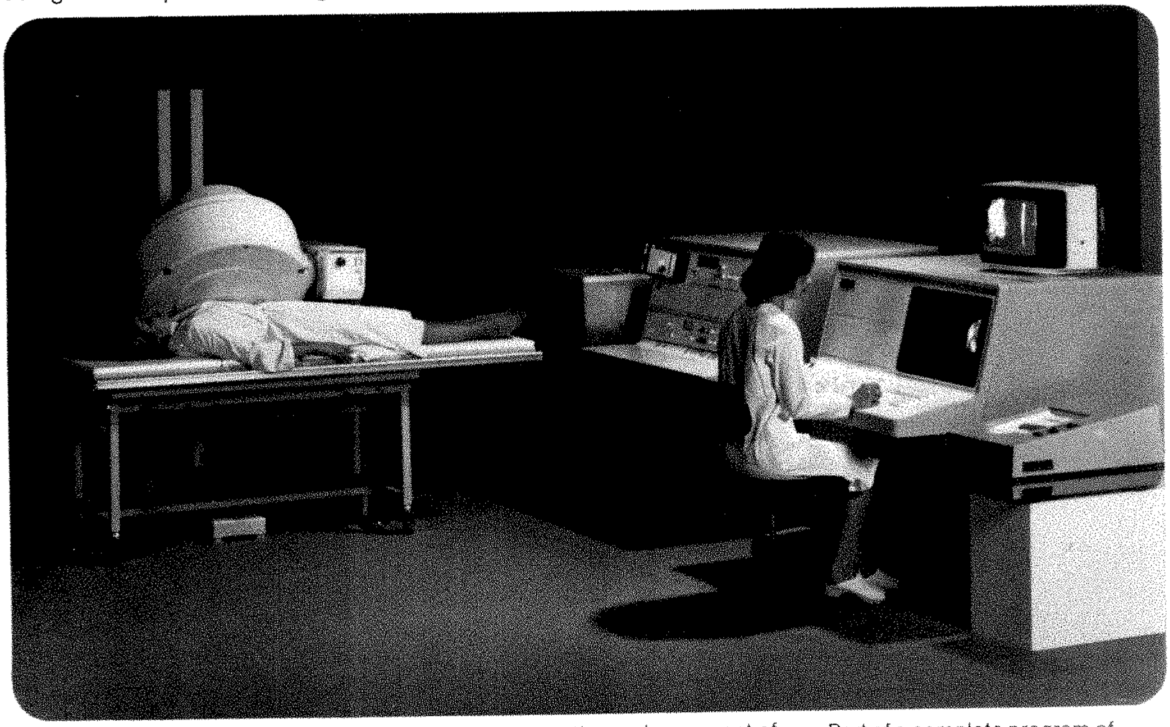

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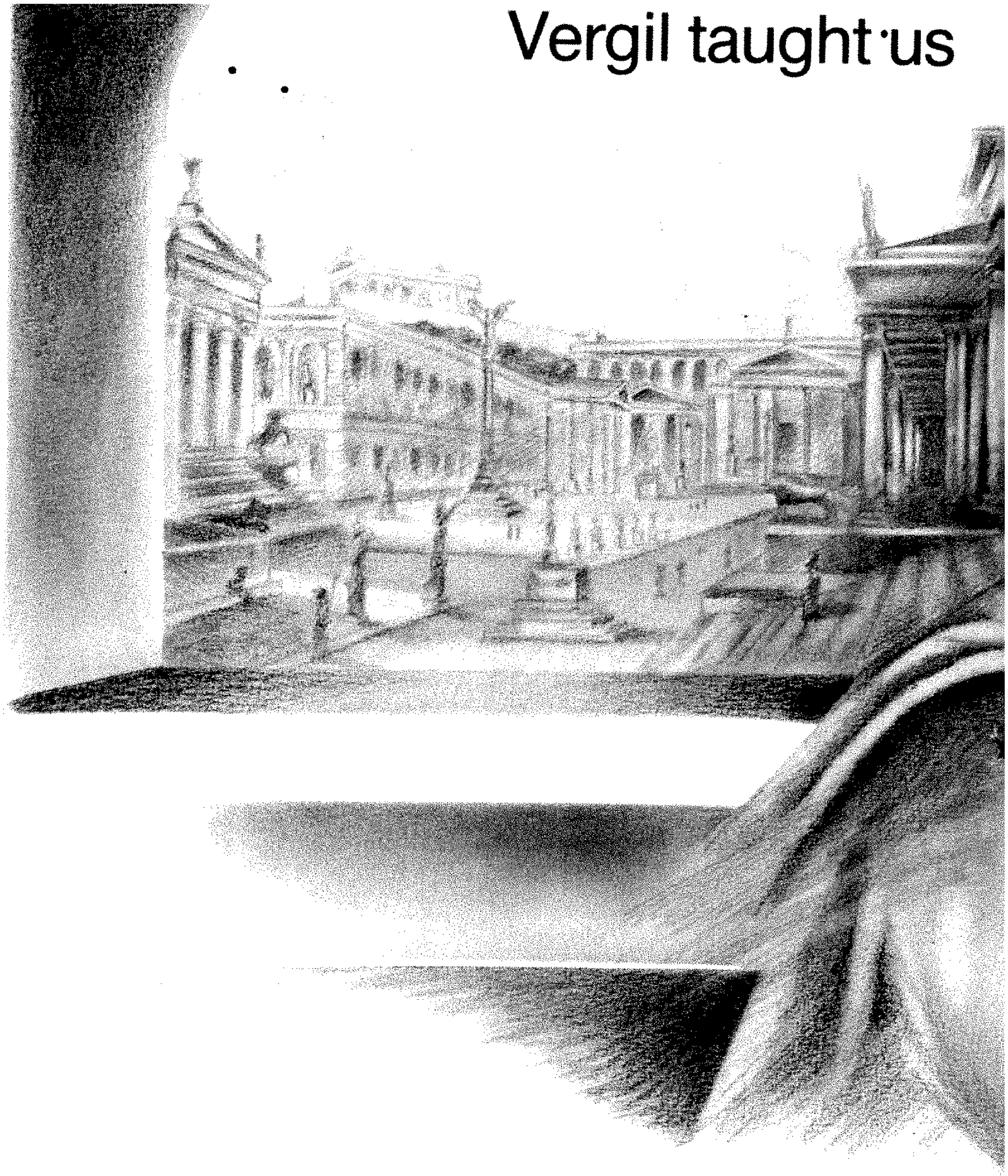

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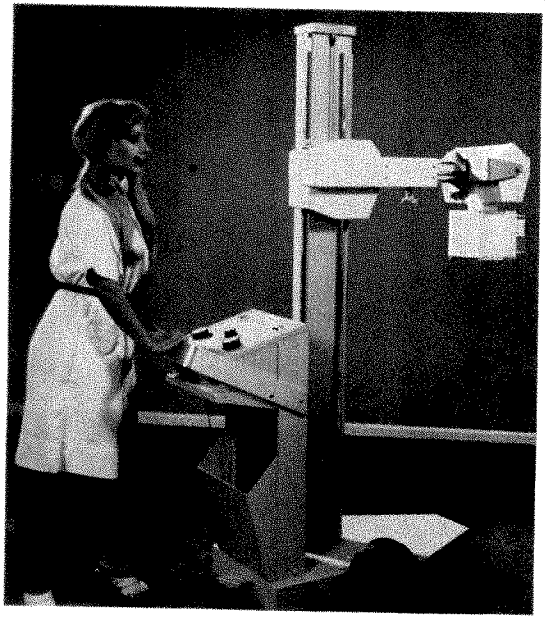

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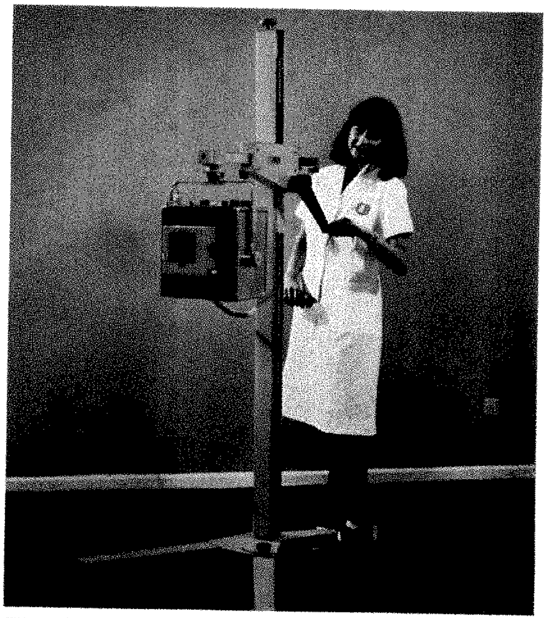

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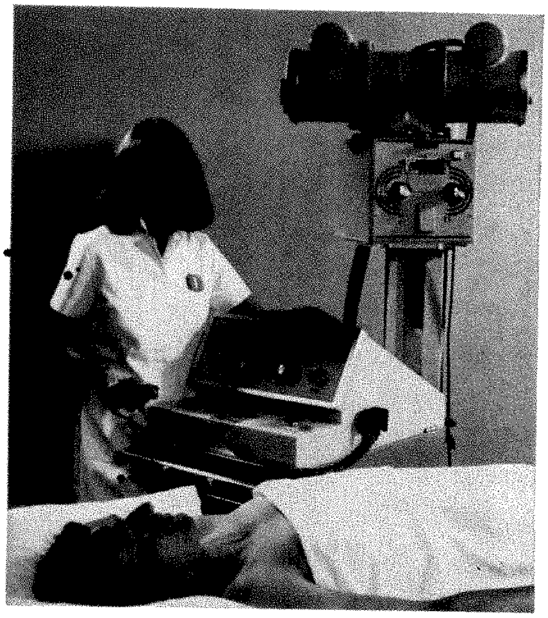

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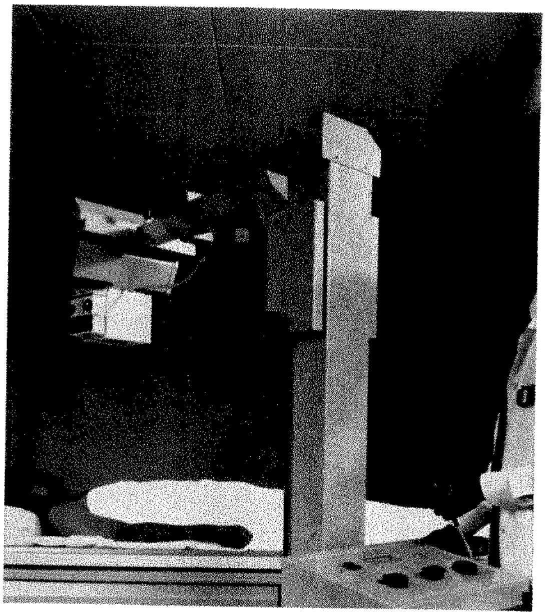

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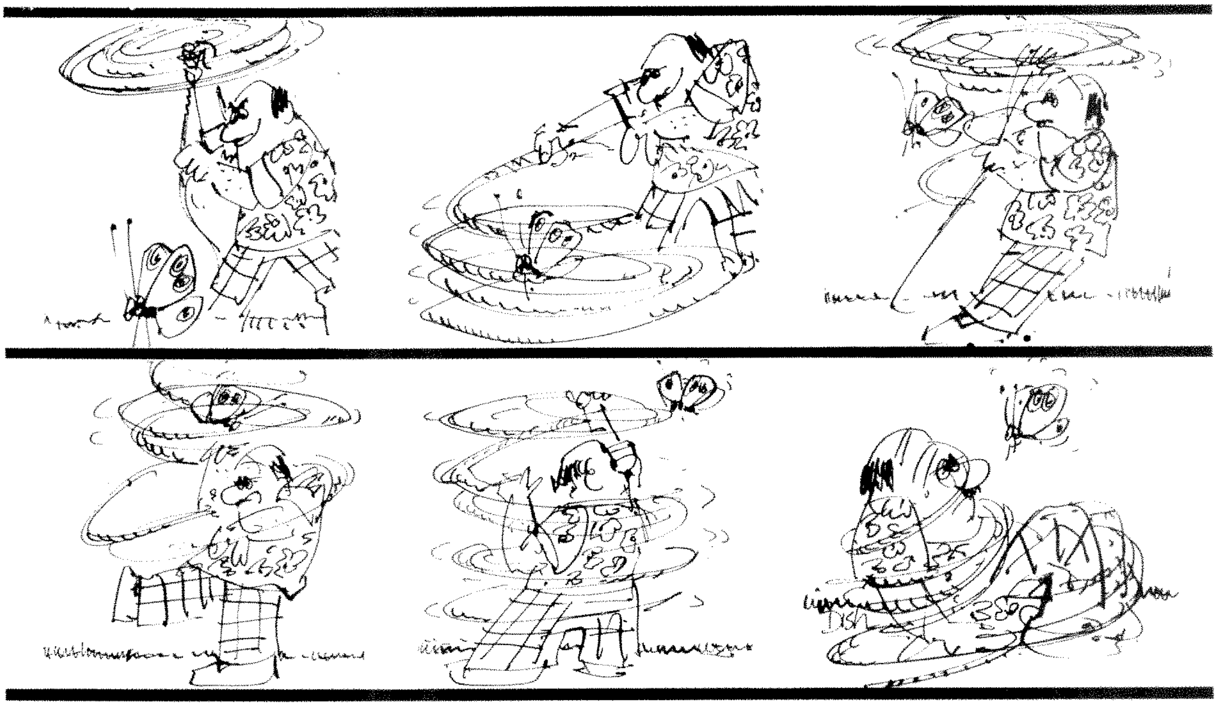

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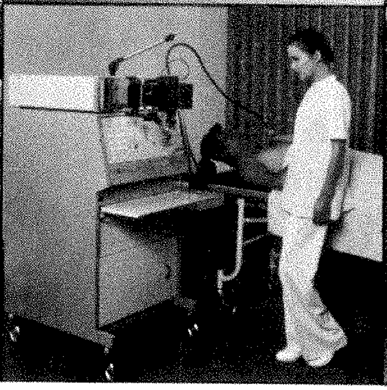

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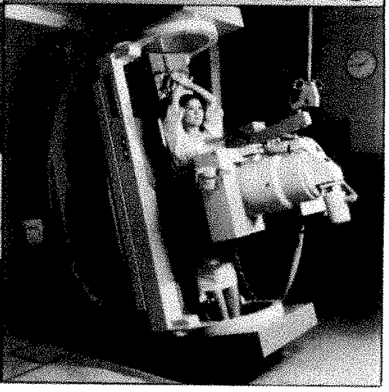

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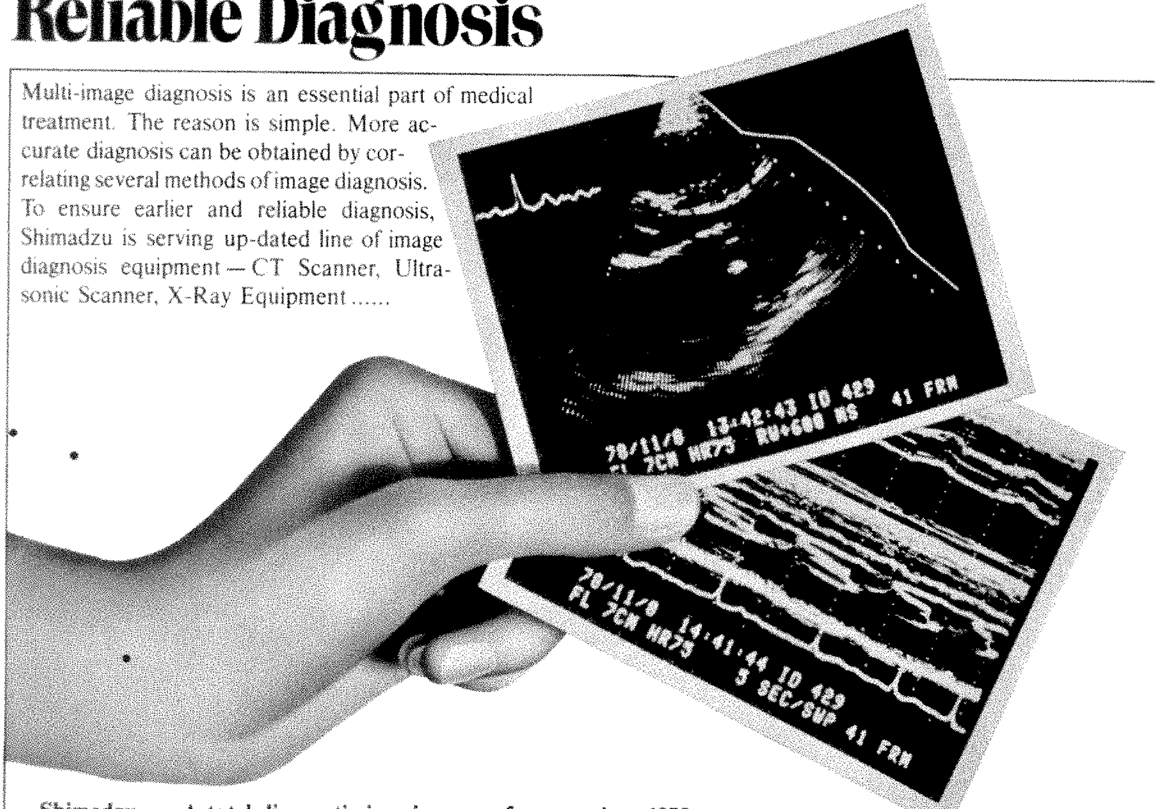

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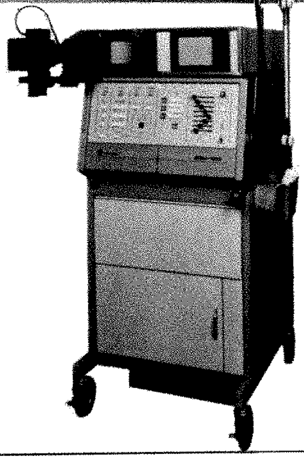

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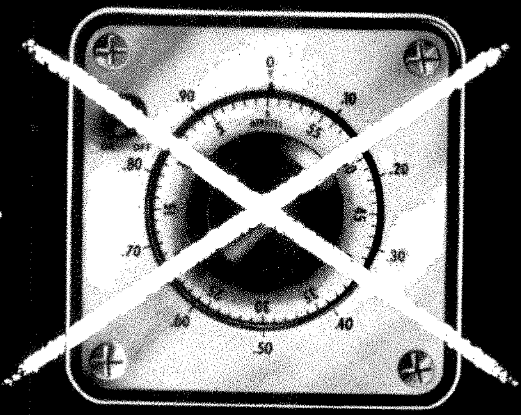

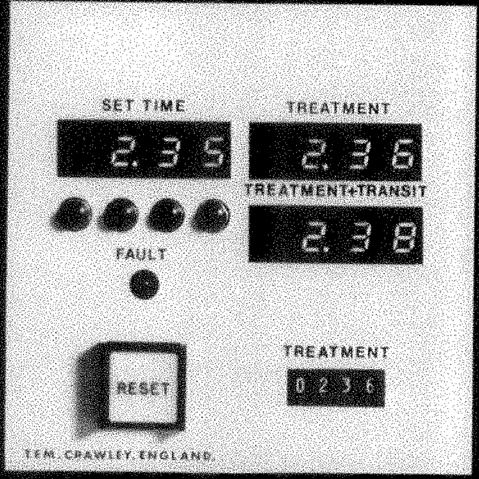

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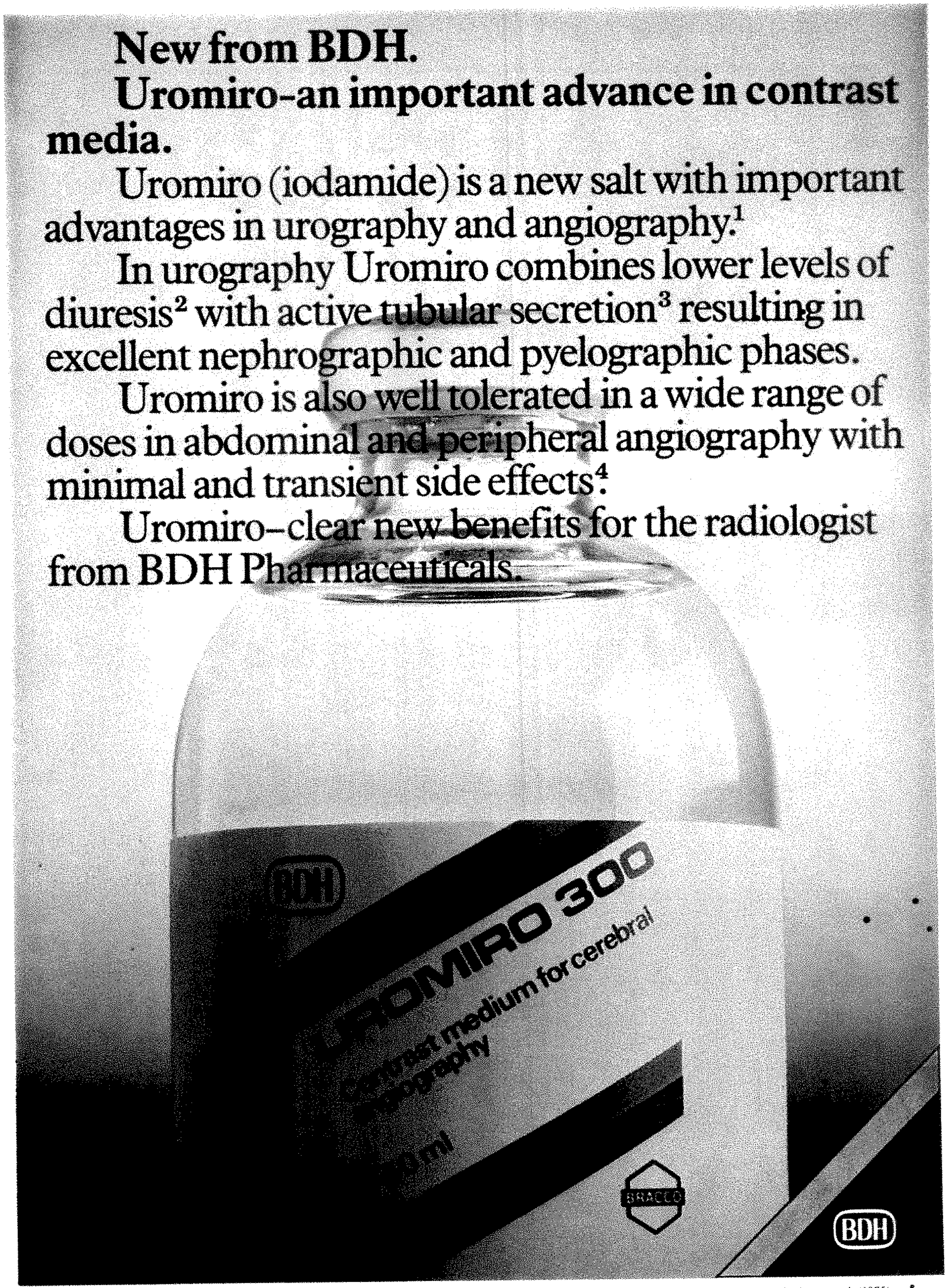

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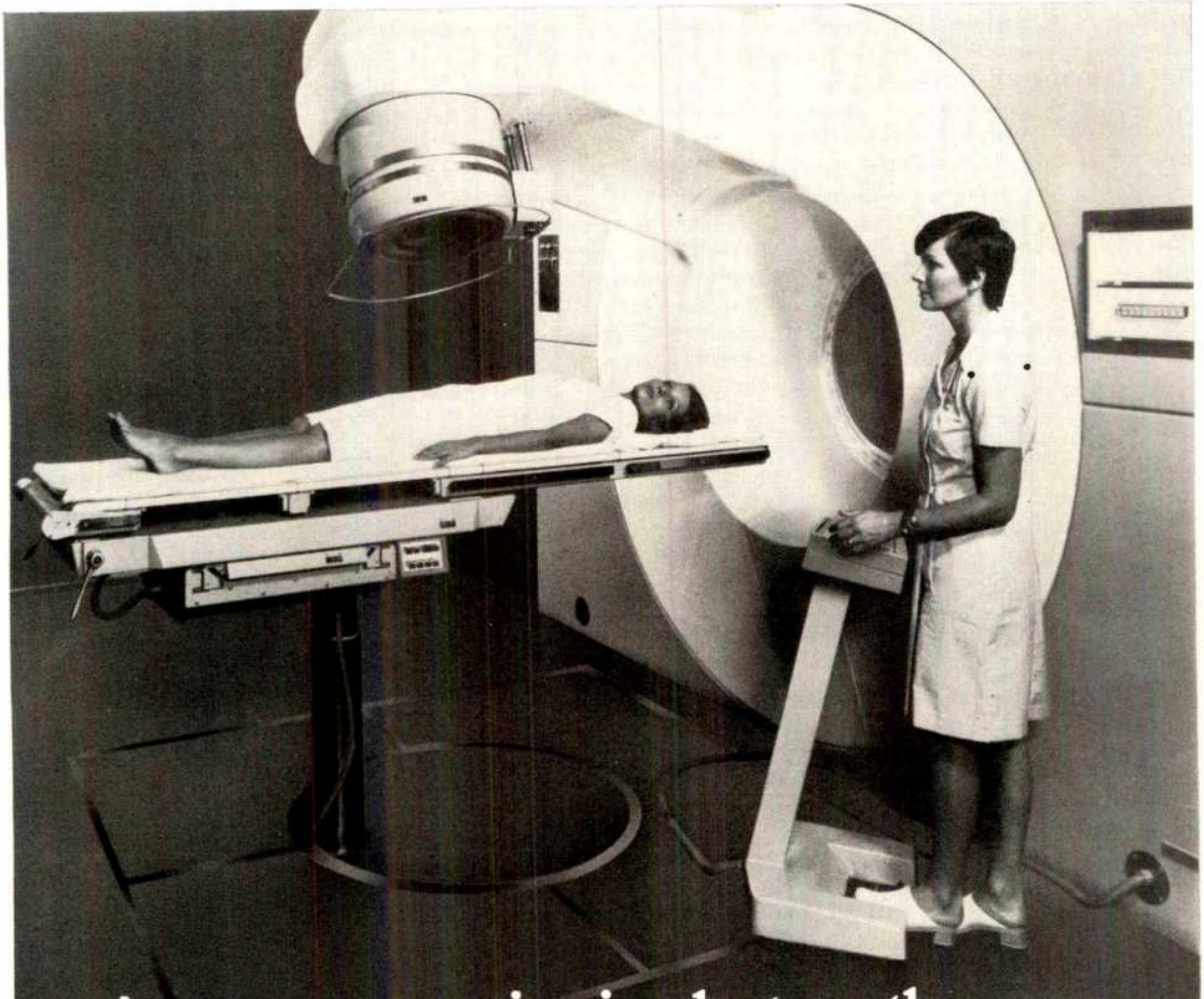

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Abstracts of free communications of 150-200 words in length on a single page should be submitted to the Organizing Secretary. These will be published as proceedings of the Congress. Deadline for receipt of abstracts is August 30th. For further information and registration contact:

Ms. Lynn E. Lindengrass,
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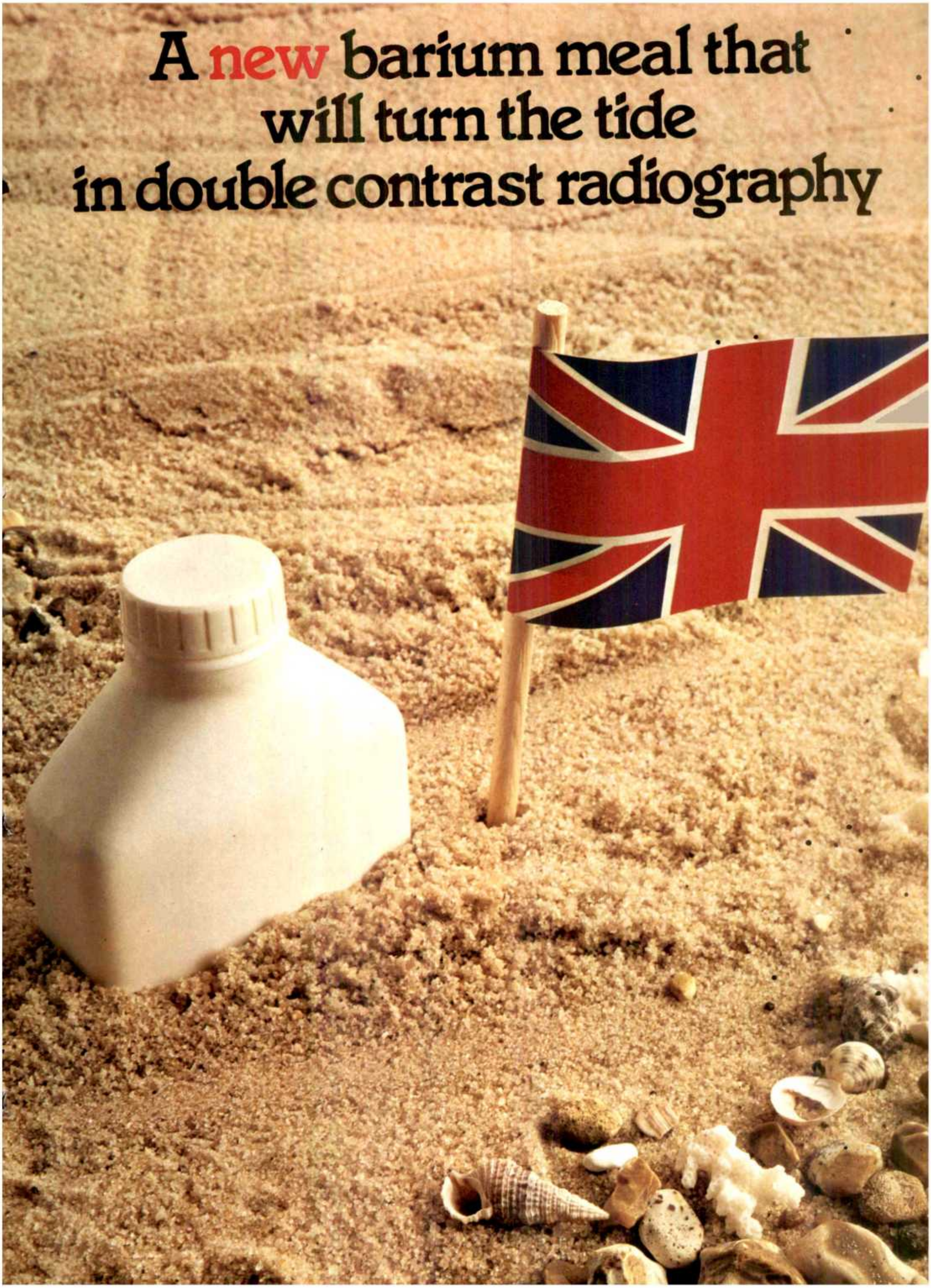

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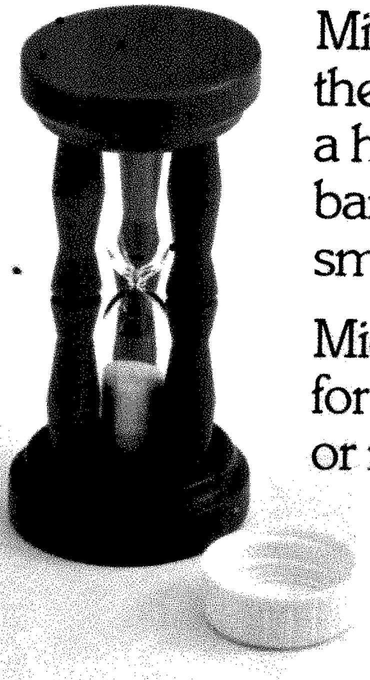

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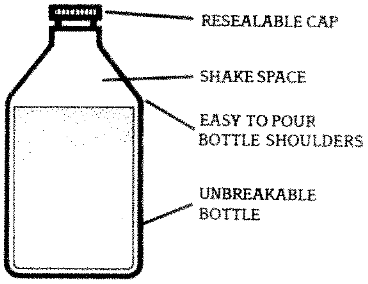

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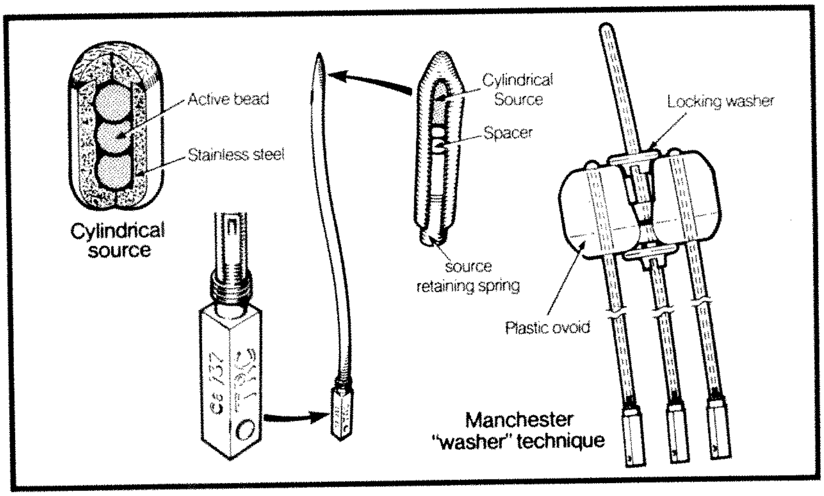

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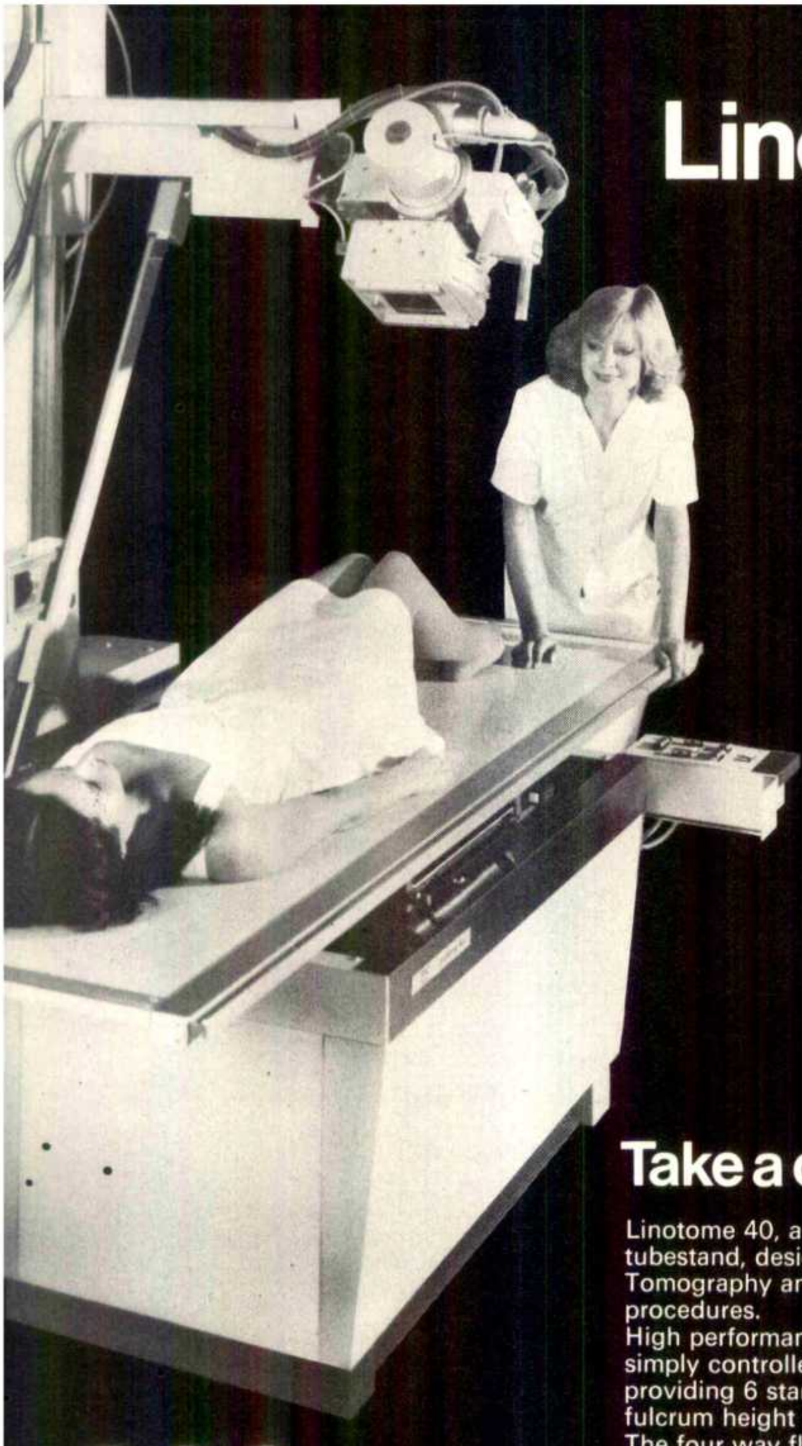

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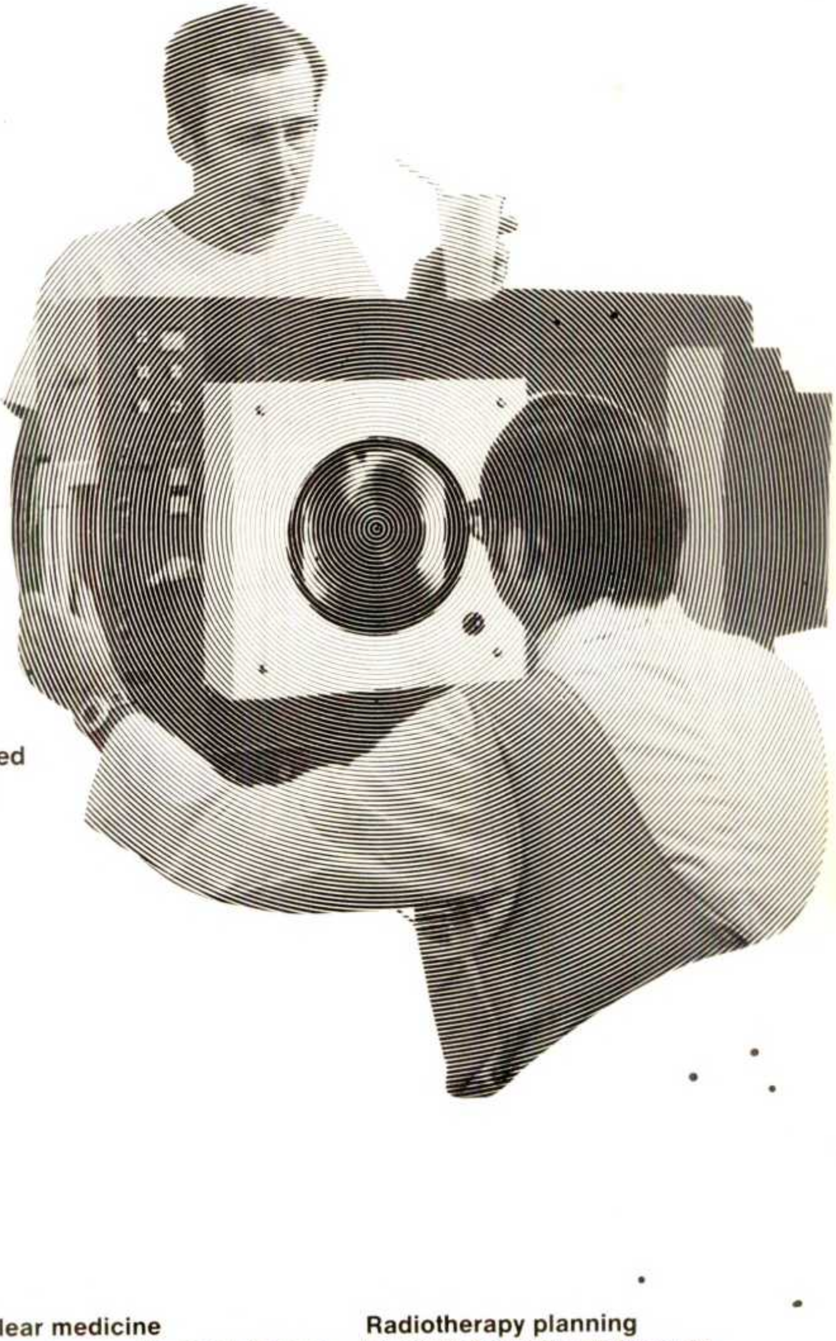

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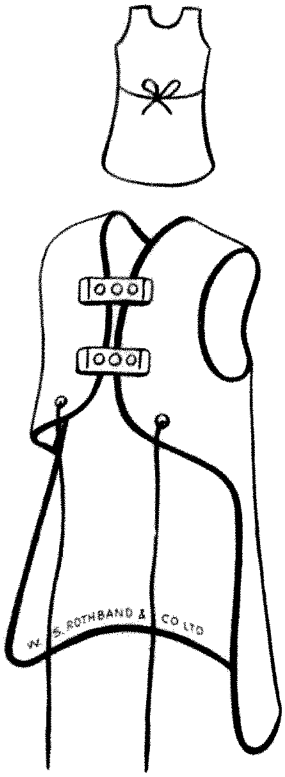
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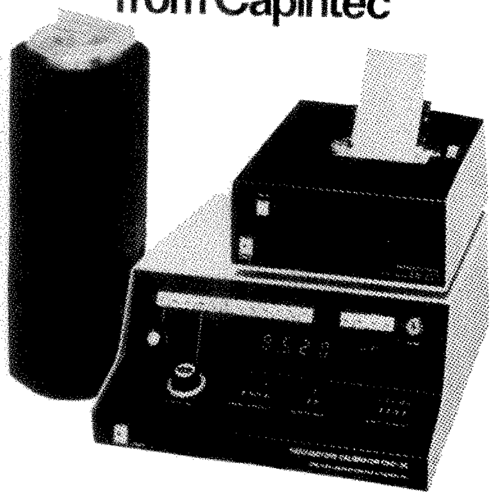

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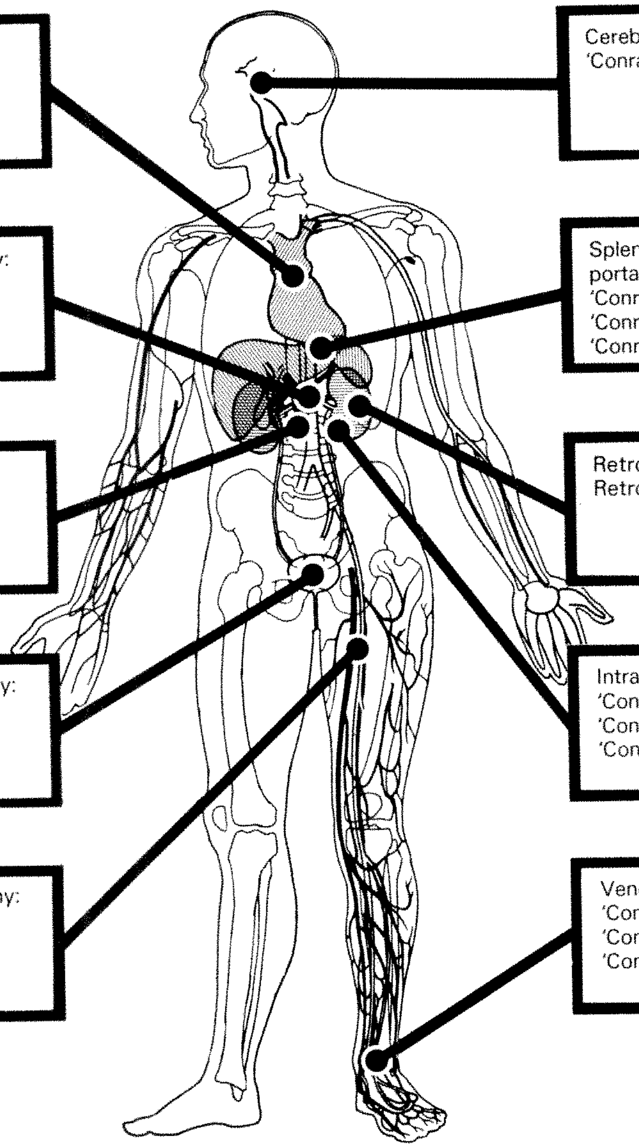

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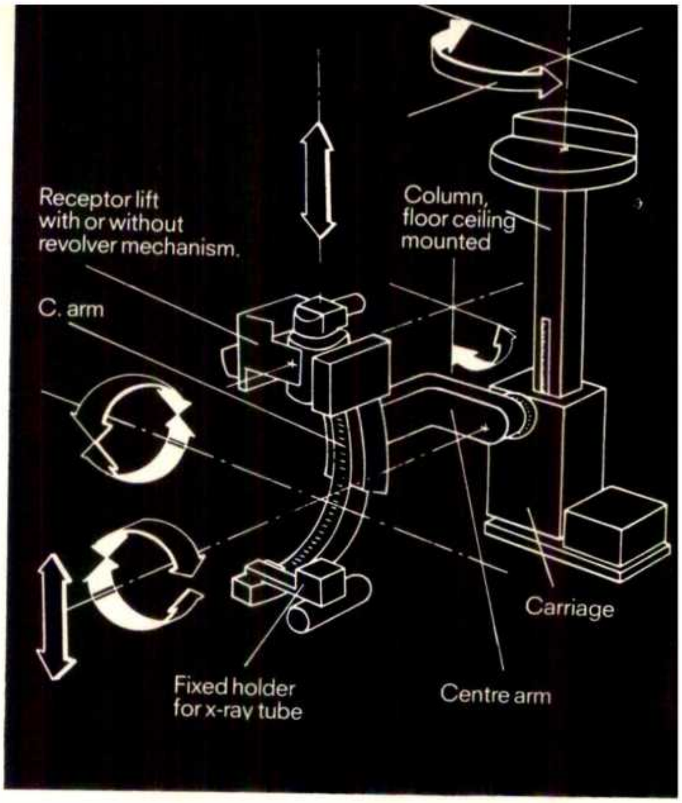
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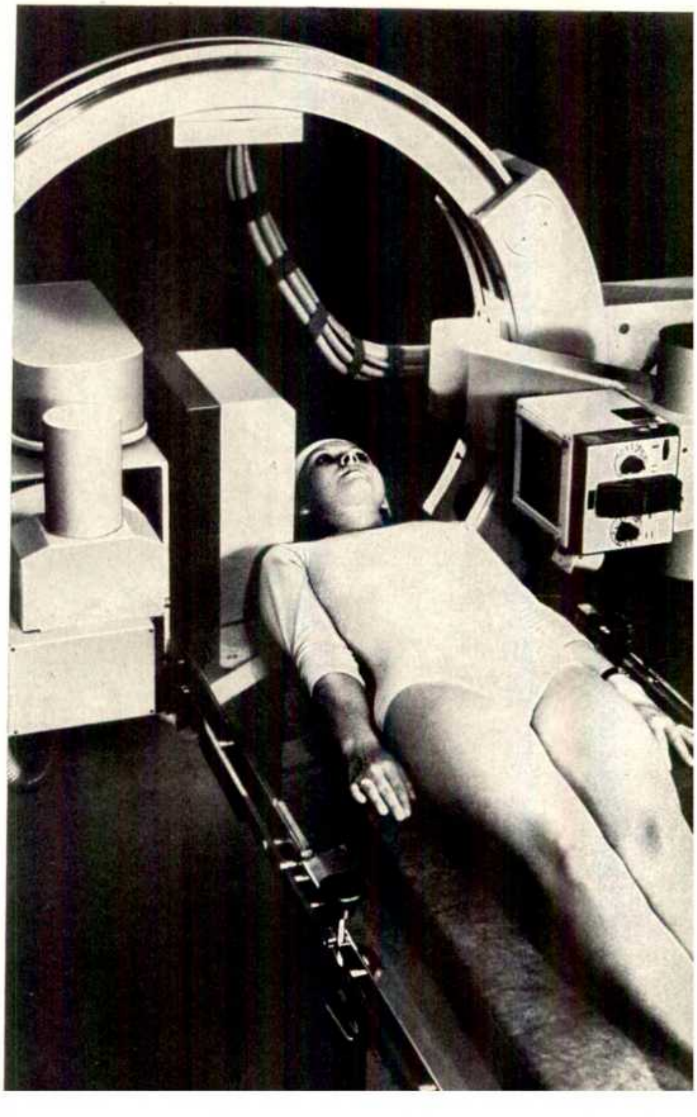

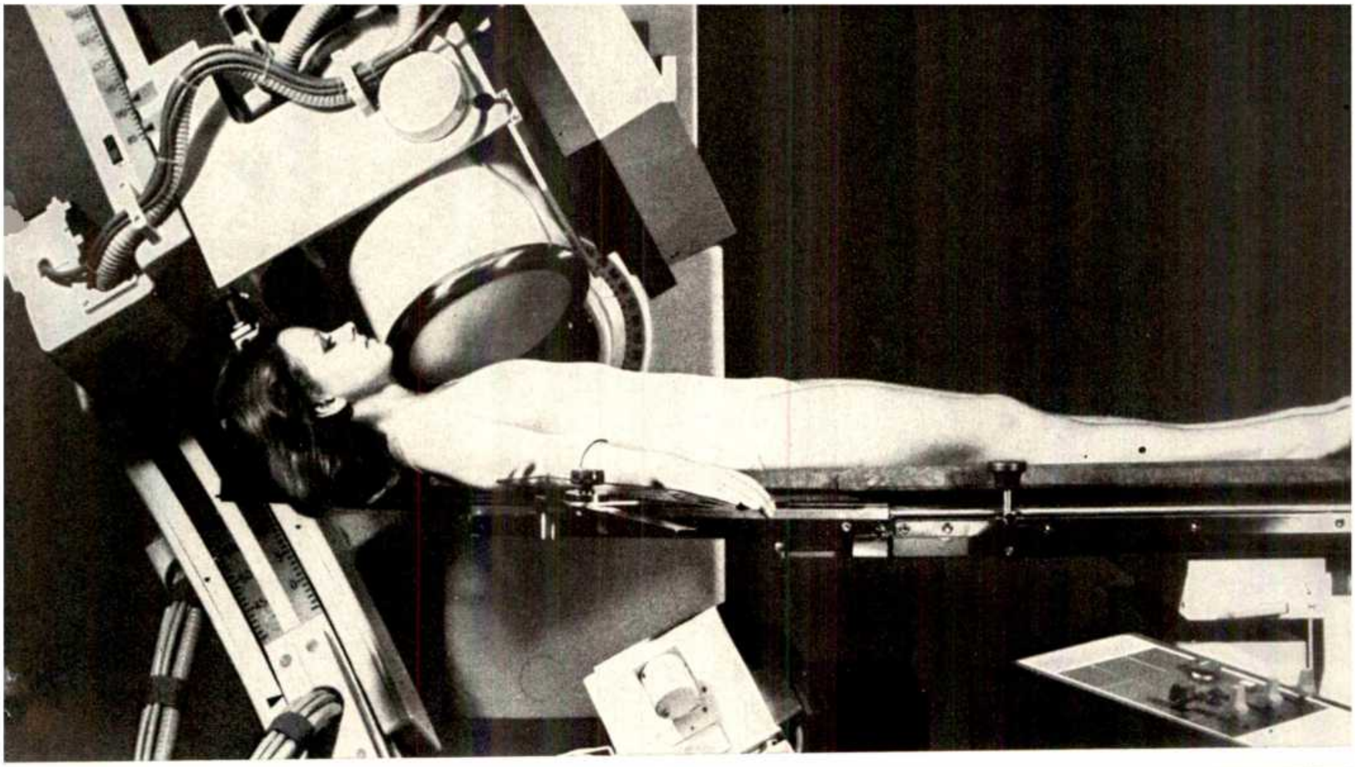

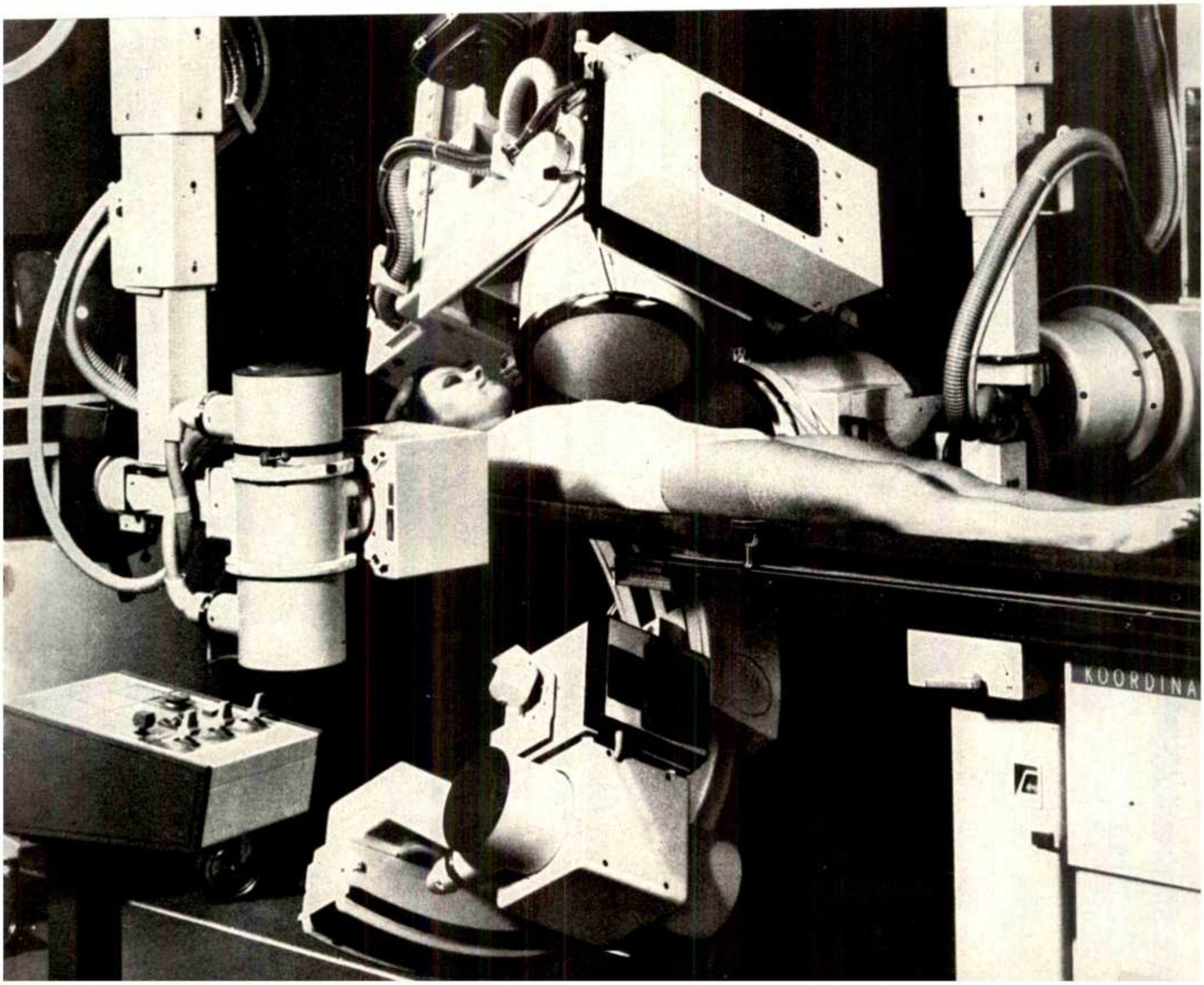

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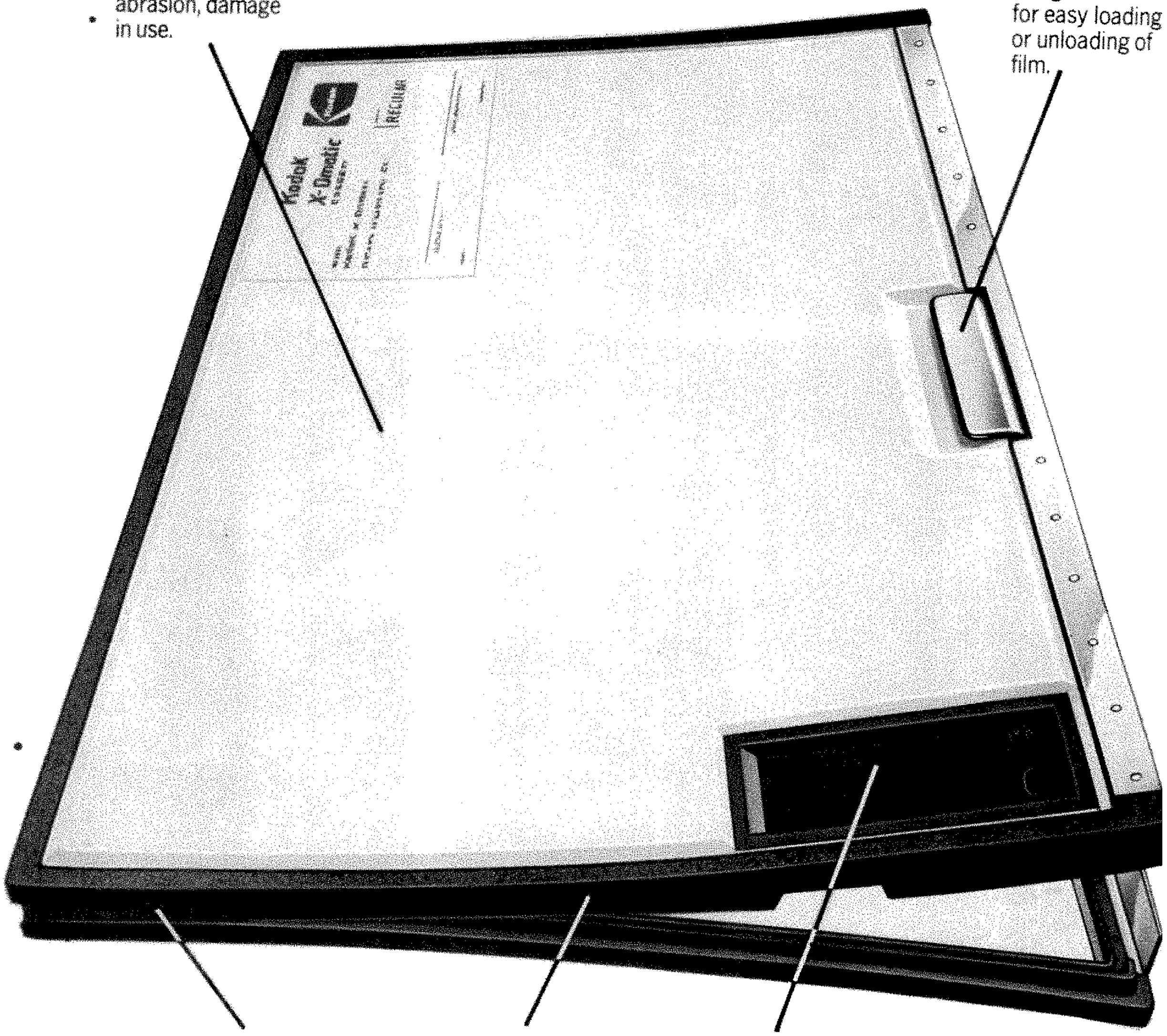

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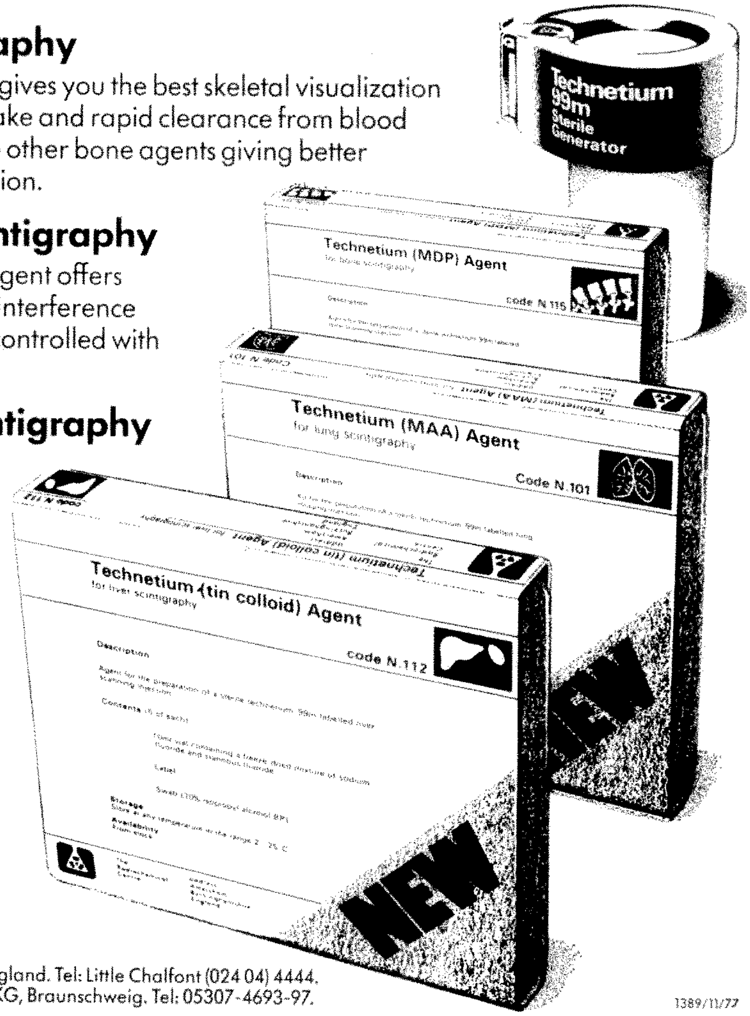

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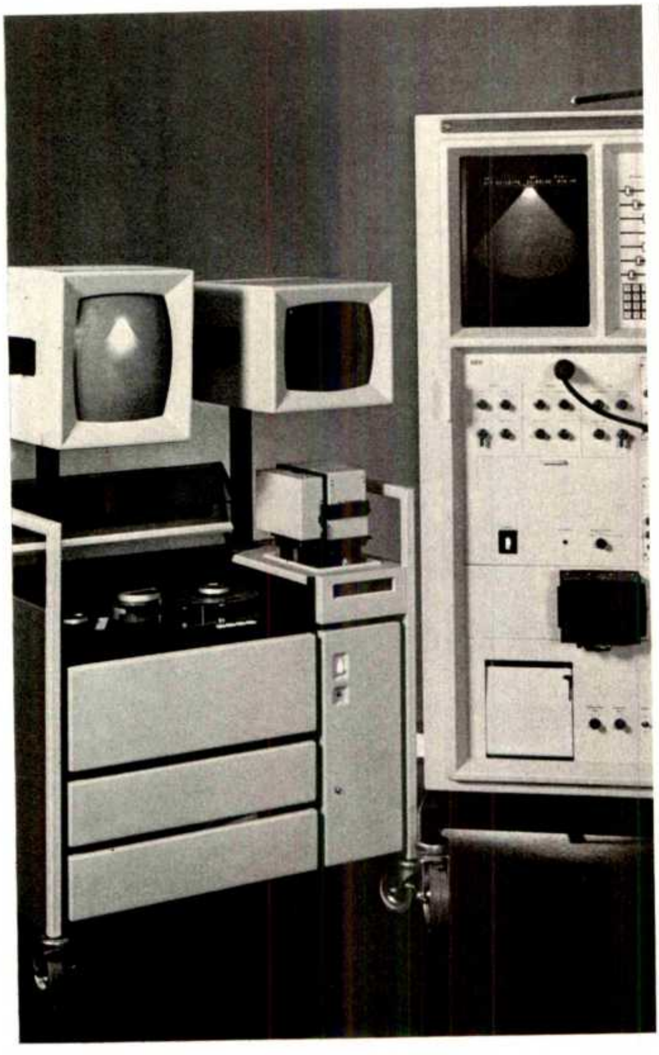

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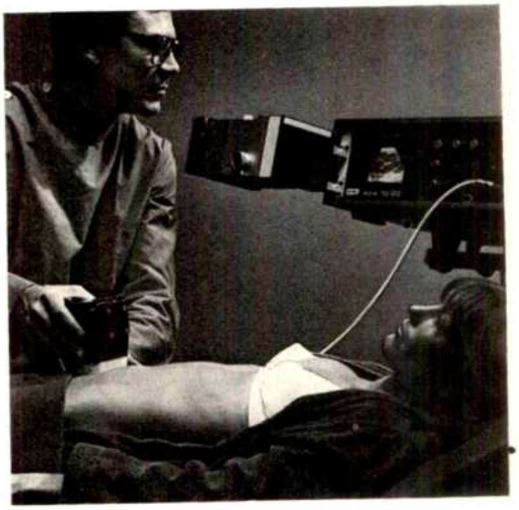

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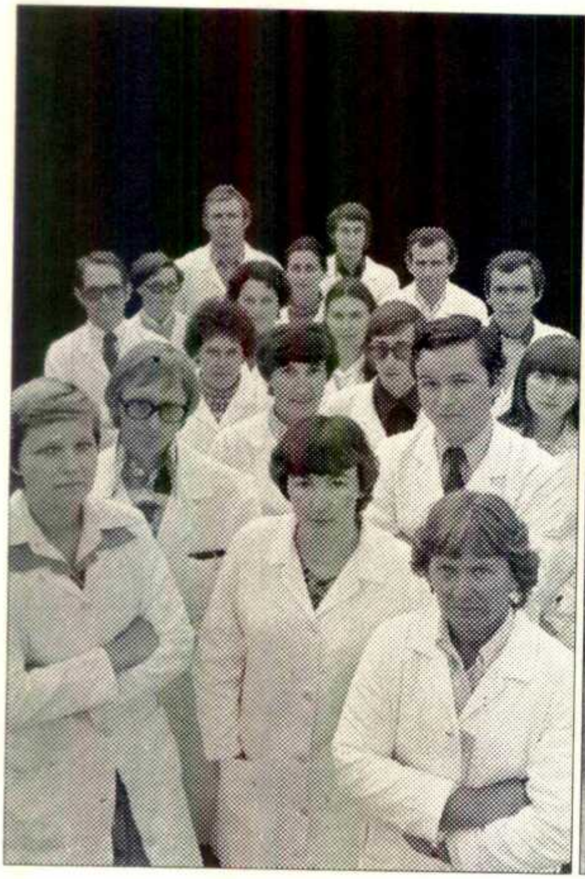

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1979, *British Journal of Radiology*, 52, 523–535

VOLUME 52 NUMBER 619 JULY 1979

The British Journal of Radiology

New horizons in radiation oncology

Presidential address delivered on April 13, 1978 at The British Institute of Radiology Joint meeting and Annual Congress held at the RIBA, London W1

By J. F. Fowler, D.Sc., Ph.D., F. Inst.P.

Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN

(*Received January, 1979*)

The scientific foundations of radiotherapy are more strongly based than for any other type of cancer treatment except possibly surgical removal of a small lump. Nowadays advances in the laboratory are put into effect in the clinic more rapidly than ever. This is illustrated by the progressively shorter time-scales of the clinical trials in hyperbaric oxygen, then neutron therapy, and now hypoxic-cell radiosensitizers. Each pre-clinical research and gestation time was shorter than the last. And yet throughout the 28 years of my association with the subject people have been saying "radiotherapy will be finished in a few years' time: cancer will be prevented by vaccines or cured by immunotherapy". However, the major advances in cancer treatment during this period have come from radiotherapy and more recently from chemotherapy and from the combination of both with surgery. This seems likely to continue in the foreseeable future, as long as patients present with a palpable lump.

No viruses have been identified as causing human cancer, although it is suspected that a limited number of types of cancer may be so caused. No immunological effect has been demonstrated on the "take" or growth-rate of tumours arising spontaneously in man or in experimental animals. It is becoming more widely recognized that valid experimental animal tumours must not be those caused by strong carcinogens or by viruses, or tumours transplanted out of their animal strain of origin, because these carry an unrealistically high immune response as a laboratory artefact.

The 80-year-old art of radiotherapy is aided as a rational speciality by the quantitative nature of its supporting scientific disciplines, radiobiology and radiation physics. Radiobiology has been called the "pharmacology of radiotherapy" and it provides a framework for teaching and for thinking about future improvements in radiotherapy. It has its own "four R's": repair, repopulation, redistribution (around the phases of the cell cycle) and reoxygenation (in tumours).

Physical dose distributions

The major gains in radiation treatment of cancer came first from physics, with better depth doses, sparing of skin, and avoidance of heavy doses from absorption in bone, as supervoltage machines were introduced in the 1950s. At present the two approaches of physics and radiobiology are "growing points" in radiotherapy from which a great deal of stimulating new work is coming. It is sometimes said that the physics objective—to increase the ratio of dose absorbed in a target volume to that outside it—has been fully achieved and that the law of diminishing returns operates in that approach. We have not reached that point yet. The argument ignores the fact that each advance in physical technology has so far found radiotherapists willing and able to develop improved ways of treating certain types of cancer. It is unlikely that no gains will result from further improvements in physical dose distribution in tissues.

There are several ways of achieving these improvements, including the apparently ultimate in high energy physics technology such as beams of negative pions or accelerated neon particles. Less expensive alternatives include proton beams, betatrons, 20 MeV electron-photon linacs, three-dimensional treatment planning, shrinking-field techniques, implanted needles or wires, after-loading techniques and computer systems.

Diagnostic and prognostic detection techniques

Improvement in physical dose distribution demands improvements in diagnostic accuracy for precise localization of tumour deposits. Here computerized tomographic scanners can help in certain sites, together with grey scale and real-time ultrasound, as reviewed in the 1978 Annual Congress (P. Morley, MacDonald, Husband, Merrick, Kirkpatrick, Van Waes and Shönfield) and improved X-ray film or ion-multiplying detectors. Developments in diagnostic techniques play an important part in improving treatment. These methods will play a further role as they become used, in conjunction with radiobiology and plasma "marker" methods, to track the success or failure of individual treatments.

The development of new methods

Figure 1 summarizes the growing points in radiotherapy (Fowler, 1977a). Some are derived from physics, some from chemistry and some from radiobiology. All of them are already undergoing clinical trials. They have been described by G. E. Adams as the five "highs" of radiotherapy: (1) hyperfractionation; (2) hyperbaric oxygen; (3) high LET; (4) hyperthermia; (5) hypodermics (chemotherapy) combined with radiotherapy. The first three of these are primarily concerned with treatment of the primary tumour. It is obvious however that as chemotherapy (or any other method of dealing with distant metastases) becomes more successful, so also must the control of the primary tumour be improved by better methods than we use conventionally today. One of the best examples of the improvement in treatment of cancer by radiotherapy is shown by the progress is treating Hodgkin's disease (Table I). In the 1940's this disease was regarded as inevitably fatal—a self-fulfilling prophecy, as Kaplan (1962) pointed out. The use of large-volume lymph-system irradiation with 250 kV X rays raised the five-year survival rate from 5% to 35%. When megavoltage beams became available in the 1950s, their physical advantages enabled the cure rate to be raised to about 70%. It was only possible to make use of the physical advantages because of the tremendous improvements in knowledge about pathways of spread in the body, obtained by sustained collaboration between surgeons and pathologists, and by developments in diagnostic radiology, especially lymphangiography. The contribution of radiobiology was to demonstrate that lymphoid tissues, including lymphoma cells, were more radiosensitive than many other types of mammalian cells, because they have a smaller shoulder on the survival curve and a fairly steep slope; so that radiotherapy was indeed a method worth taking time and trouble to develop. The radiotherapists demonstrated that a high proportion of these patients could be cured, and that, with carefully developed techniques of beam-definition and local shielding, normal tissue complications could be kept to an acceptably low proportion. This was an admirable example of collaboration between determined and scientifically-minded radiotherapists,

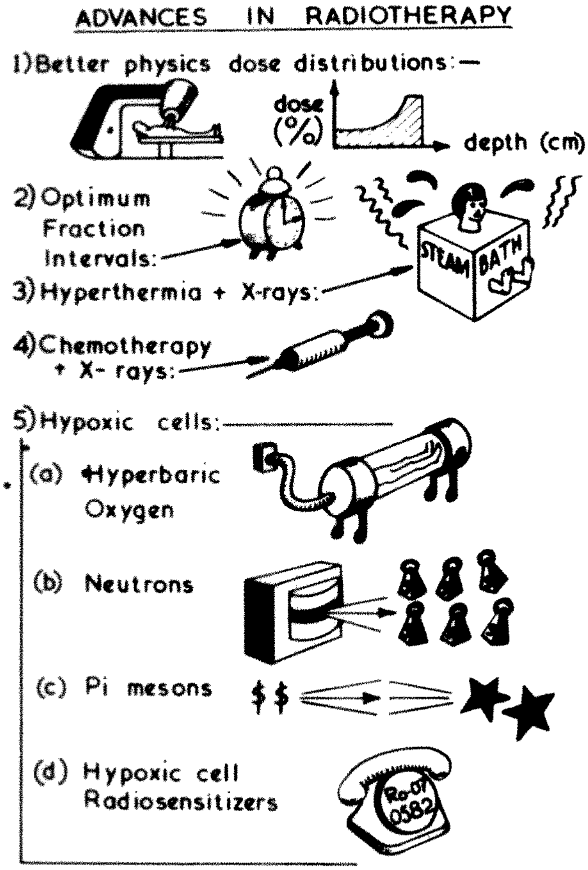
ADVANCES IN RADIOTHERAPY
1)Better physics dose distributions:—
dose (%)
depth (cm)
2) Optimum Fraction Intervals:
3) Hyperthermia + X-rays:
STEAM BATH
4) Chemotherapy + X-rays:
5) Hypoxic cells:
(a) Hyperbaric Oxygen
(b) Neutrons
(c) Pi mesons
$$
(d) Hypoxic cell Radiosensitizers
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Fig. 1.

Some of the present growing points in radiotherapy (Fowler, 1977a).

TABLE I

Improvement in 5-year survival from Hodgkin's disease

Date	Treatment	5-year survival
1940	Considered inevitably fatal	5%
1960	250 kV X rays	35%
1970	Supervoltage mantle with exploratory surgery and lymphangiography	73%
1974	Supervoltage plus chemotherapy	79%

physicists, surgeons, pathologists and diagnostic radiologists. But there is yet more collaboration to relate: the addition of quadruple chemotherapy has raised the five-year survival rate to nearly 80%.

Clinical trials

The sequence of advances in treating Hodgkin's disease, taking place in steps over some 20 to 30 years, seems to be a likely pattern for improvement in treating other types of cancer. It requires willing collaboration between specialities, the gradual collection and careful analysis of pathological and clinical data, and above all the determination to improve results. It also requires patience, as does much else in cancer research. The difference between 5% and 79% survival rate is easy to demonstrate with statistical significance but it occurred at an average rate of only 3% per year. Since an improvement of about 20% requires several hundred patients before it can be substantiated (Boag *et al.*, 1971), no "proof" that clinical progress was being made could be expected in less than six or seven years. This remains true for future methods.

It is necessary to pay more attention to the reliable collection of data on results of cancer treatment. Every patient treated should contribute in some way to the pool of data. Real improvements in clinical results could then be recognized at the earliest opportunity and false claims would not receive undue publicity.

Fractionation in Radiotherapy

It has long been suggested that one of the reasons for the successes of multiple-small-dose radiotherapy might be that cells in the tumour are less capable of repairing sublethal injury than cells in normal tissues, although reviewers have not agreed on this (Withers, 1970; Field, 1970; Phillips, 1972; Denekamp and Stewart, 1979). One reason for this was suggested by Littbrand and Revesz (1969) on the basis of loss of repair capability if cells are deeply anoxic, with an oxygen tension as low as 5 ppm (Pettersen *et al.*, 1973). However, whether such low levels of hypoxia exist *in vivo* is not known. Hill and Bush (1976) have suggested slower repair in mouse tumours than in normal tissues, so that at three or four hours after a dose of X rays, cells in normal tissues would have repaired their sublethal radiation injury but cells in tumours would not. These straws in the wind have led to the clinical use of two or three small doses of X rays on each treatment day in a number of centres including Houston, Boston, Vancouver, Stockholm, Göteborg, Portsmouth, Rome and Bologna. No adverse reports have yet been made although we shall have to wait the usual six or seven years after starting before definitive reports can appear. The studies have been under way for more than five years in some of the centres and preliminary results have been reported. For example Littbrand from Stockholm, using 84 fractions of 100 rad each (given at three per day over six weeks with a gap in the middle) has reported better local control of bladder carcinoma and better survival of the patients than with the conventional 32 × 200 rad treatment (Littbrand, 1975; 1978) although these results must be regarded as still preliminary. Douglas in Vancouver (Douglas, 1977) has reported an increased mean survival time for brain tumour patients treated with 60 fractions given as 3 × 100 rad per day over four weeks, as compared with a historical control group of previous patients given 20 fractions in the same overall time. During the last week of treatment he used smaller sized fields. Turesson and Notter (1976) in Göteborg have shown that acceptable levels of skin reaction can be obtained using three doses per day and that the late skin reactions that follow are only a little greater, not significantly so, than the usual expectation (Turesson, 1978). (This does not seem to be true for either two fractions per week or for very extended schedules exceeding seven weeks overall time, when late reactions are appreciably greater than might have been expected from the early ones.)

The schedules described above make use of several X-ray doses per day and are called superfractionation or hyperfractionation. One reason for employing this approach is the assumption that less repair of X-ray damage occurs in tumours than in normal tissues. What can radiobiology contribute to this idea?

Evidence has been obtained that the capacity to repair X-ray injury in some types of mouse tumour at 24 hours is less than in normal tissues and that this might result from a steeper initial slope to the survival curve for tumour cells (Denekamp and Stewart, 1979). However, this is not a uniform finding in all types of mouse tumour studied. Further work is required on the physiological and biochemical conditions which lead to less or slower repair.

At the other extreme, where only one or two radiation doses may be given each week, recent clinical evidence has been reported in the literature that two fractions per week cause more damage to normal tissues than would be expected either from the usual NSD formula or from doses yielding local control of tumours as good as that from conventional daily fractionation (Bates and Peters, 1975; Withers *et al.*, 1978). The implication leads in the same direction as the previous paragraphs: towards a preference for multiple small fractions. Superfractionation means that the overall time need not be extended and might even be shortened.

One further remark concerning overall time in fractionation schedules is worth noting. Where the limiting radiation damage is late injury, these tissues must be turning over very slowly, or their damage would be expressed sooner. It would therefore make little difference to injury in these tissues whether the overall time is two weeks or ten, if proliferation is the only factor which requires more dose when the overall time is lengthened. They will not proliferate in any case during the radiation treatment time (Denekamp, 1975; Denekamp and Fowler, 1977).

However, the phenomenon of slow repair (Field and Hornsey, 1976; 1977) explains in a different way why lengthening the overall time also causes a reduction in late injury. This reduction will be smaller than for acute skin reactions, because slow repair occurs mostly in the first two weeks after starting irradiation whereas accelerated proliferation in acutely reacting tissues occurs after this time (Denekamp, 1973). By the same argument, shortening the overall time (to say one-half) will not increase late injury as much as it will increase acute reactions.

Therefore when late injury is what limits the radiation dose level, there should be more flexibility in choice of overall time than the traditional "rules of thumb" (often based on acute skin reactions) have allowed. This is important when we consider below the suggestions to shorten overall treatment times provided that hypoxic cells can be effectively dealt with.

METHODS OF DEALING WITH HYPOXIC CELLS

The much greater resistance of hypoxic cells to X rays has been recognized for many years as one possible reason for the failure to control tumours locally (Gray *et al.*, 1953). The presence of hypoxic cells in both animal and human tumours is accepted on histological grounds (Thomlinson and Gray, 1955) but the continued presence of hypoxic cells throughout a course of radiotherapy has been questioned because of possible reoxygenation in the tumour (Thomlinson, 1969; Van Putten and Kallman, 1968).

Hyperbaric oxygen

The recent results of the MRC hyperbaric oxygen (HBO) trials have shown unequivocally that hypoxic cells are present in human tumours, at least of some types, and are a problem even in treatment schedules using 25–30 small fractions of X rays. Table II summarizes these results from the use of HBO in cancer of the uterine cervix (Watson *et al.*, 1968). The results for local control at five years are significantly better for HBO. Table III shows similar results for head and neck cancer (Henk *et al.*, 1977; Henk and Smith, 1977). No improvement was seen, however, for Ca bladder when HBO was used. In both the cervix and head and neck trials the increase in local control was about 20%. Because of distant metastases the increase in survival was smaller than the increase in local control but was just statistically significant ($P < 0.05$) for Ca cervix Stage III, and also for the second head and neck HBO trial if the Leeds and Cardiff cases were pooled. In the latter trial no increase of normal tissue damage was reported for HBO as compared with conventional radiotherapy.

There are physiological reasons for thinking that HBO might not be the best way to combat hypoxic cells. Higher oxygen tension in tissues causes vasoconstriction so the method may be self-limiting (Lambertson, 1966; Milne *et al.*, 1973). In addition the method is time-consuming for staff and for radiotherapy equipment. Other methods of dealing with hypoxic cells must also be sought.

Fast neutrons

Figure 2 shows that the protection afforded by hypoxia varies with the linear energy transfer (LET) *i.e.* the ionizing density of the radiation used to treat cells (Barendsen, 1968). The difference between irradiations in oxygen or in nitrogen, termed the OER, is a measure of this effect. For lightly ionizing (low LET) radiation such as X or γ rays the OER is 2.5–3.0, but this falls to a value of about 1.7 for fast neutrons, negative pi mesons and heavy charged particles up to neon ions. All these particle beams are in reality a mixture of high and low LET, the low LET having an X-ray-like value for the oxygen effect, which prevents an overall OER as low as unity from being achieved. Any reduction in the OER, however, will reduce the radioresistance of hypoxic tumour cells and should be an advantage in radiotherapy.

There are three main radiobiological differences between high and low LET radiation:

(1) The OER is reduced with increasing LET.

(2) The capacity for repair of sublethal radiation injury is lower after high LET irradiation.

(3) There is less variability in radiation response between different phases of the cell cycle after high LET irradiation.

TABLE II

MRC HYPERBARIC OXYGEN TRIAL. CARCINOMA OF CERVIX UTERI STAGE III

	HBO	Air	Comments
5-year survival			
(6F) Portsmouth (37 pts)	42%	17%	In-air results were poor
(6F) Oxford (23 pts)	46%	8%	
(25F) Glasgow (127 pts)	50%	37%	Combined, $P < 0.05$
(30F) Mt. Vernon (56 pts)	39%	28%	
Local control 5 years			
Glasgow	87%	60%	Highly significant differences
Mt. Vernon	76%	50%	
Severe morbidity			
Bowel	12%	4%	

TABLE III

MRC HYPERBARIC OXYGEN TRIAL. CARCINOMA OF THE HEAD AND NECK

	HBO	Air	Comments
1st trial (276 pts)			
Local control (5 years)	53%	30%	$P < 0.001$
Survival (5 years)	40%	40%	Saved by surgery
2nd trial (103 pts)*			
Local control (2 years)	65%	47%	$P < 0.05$
Survival (2 years)	71%	50%	$P < 0.01$

*No difference in complications. 10% lower dose to larynx fields only.

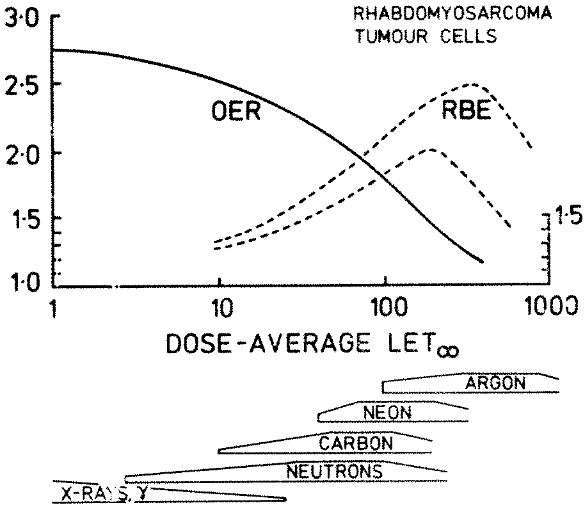

FIG. 2.

As the linear energy transfer (LET) of radiation increases, the relative biological effectiveness (RBE) rises to a peak then falls again. The oxygen enhancement ratio falls. The trapezoids at the bottom indicate the approximate range of LET present in each type of radiation (Curtis, personal communication).

The first is an obvious advantage in the treatment of any tumours with hypoxic cells present. The second could be either an advantage or a disadvantage, depending on the relative loss of repair capacity in tumours and normal tissues. The third would be an advantage when more of the tumour cells than the normal cells are in S-phase (*i.e.* dividing).

The early use of fast neutrons by Stone (1948) resulted in some striking tumour regressions but also in severe late normal-tissue complications, which postponed further clinical studies for nearly 20 years. In the early 1960s, however, pig skin was used to demonstrate that severe normal tissue complications were avoidable (Fowler and Morgan, 1963; Bewley *et al.*, 1963), and the reason for Stone's disastrous results was shown to be the lack of knowledge at the time that the relative biological effectiveness of neutrons (RBE) depended upon the size of individual dose fractions (Field, 1970; Sheline *et al.*, 1971). The RBE is higher for the small doses used in fractionated treatments than for the large single doses used in Stone's pilot studies on patients. This is an example of inadequate radiobiology delaying the field for 20 years. A new wave of interest in neutron machines followed this explanation of Stone's late complications. Recently Catterall *et al.* (1975; 1977) have reported the results of the clinical trial carried out at Hammersmith on advanced head and neck cancer using the MRC cyclotron (16 MeV deuterons on a beryllium target). Figure 3 illustrates these results. The local control of tumours was increased from 19% to 76% using neutrons instead of photons. This is a large and highly significant increase.

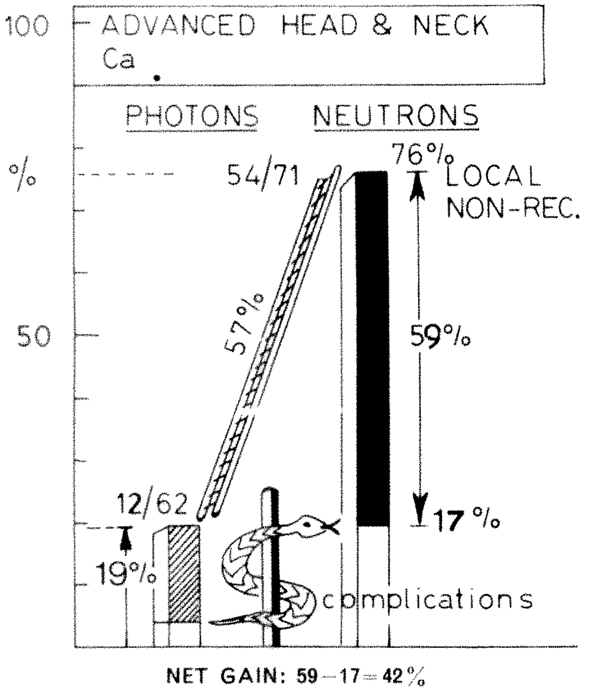

Fig. 3.

Results of the clinical trial of advanced head and neck cancer at Hammersmith Hospital (Catterall *et al.*, 1977).

TABLE IV

Fast neutron clinical trial advanced head and neck Ca. (Catterall et al., 1975, 1977)

Subdivision of patients to compare local control if non-Hammersmith treated patients or lower photon dose groups are excluded

Local control of tumours	Photons	Neutrons	P
(1) All patients	12/62 (19%)	54/71 (76%)	< 0.001
(2) Hammersmith patients only	5/25 (10%)	18/20 (90%)	< 0.001
(3) Patients receiving 110–130 TDF only	3/12 (25%)	53/68 (78%)	< 0.01
(4) Patients receiving 110–120 TDF only	3/11 (27%)	30/37 (81%)	0.024

Some of the photon patients received rather low doses of radiation, but even if these are excluded from the comparison, the neutrons still show a similar and significant increase in local control. Table IV shows this and provides a clear answer to some criticisms of that trial. However there was also an increase in severe complications from 4% to 17%; this is the aspect of the trial that seems worrying to many critics. It does not allow us to judge whether the improvement simply results from a higher biologically effective dose to both tumours and normal tissue. However, the final statistical analysis in actuarial terms has not yet been completed: this will compare complications per patient at risk instead of per patient entering the trial. Since there was a small increase in mean survival time of the patients treated with neutrons, the actuarial method will yield a smaller difference in complications than the figures given above. For example, if all the complications occurred only in those patients in whom the primary tumour was locally controlled, the ratio of complications to number of patients with locally controlled tumours would be $2/12=17\%$ for neutrons and $10/53=19\%$ for the photon controls. This difference is not significant, and before we can discuss it further the full actuarial analysis must be completed. The point is that a prohibitively high incidence of late normal tissue injury, as once alleged by Stone (1948), is not supported by the present clinical data.

Some of the neutron complications may be attributed to the fixed horizontal beam with less good physical penetration than ^{60}Co γ rays, others to the fact these very advanced tumours had eaten away large volumes of normal tissue so that successful tumour regression left a large cavity. It remains to be shown whether a neutron beam of good physical properties, comparable in depth dose and penumbra to megavoltage X rays, can maintain such a dramatic increase in local control as shown in Fig. 3 with less increase in normal tissue complications. Although fast neutrons are being used or are about to be used clinically in some 20 centres in ten countries, only two are providing a neutron beam with a depth dose as good as that of X rays from an ordinary 4 MeV linear accelerator. There cannot be a satisfactory clinical evaluation of fast neutrons until such beams are used because the present physical disadvantages may offset the biological advantages.

Negative pi mesons and heavy particle beams

In addition to the biological advantages of high LET radiation mentioned above, some beams of nuclear particles also provide an ideal physical depth dose distribution (Fig. 4). More dose is deposited at depth than in the overlying tissue along the entrance path of the particles, *i.e.* there is a Bragg peak which can be spread out in depth over several centimetres. This is expressed by saying that the "peak to plateau ratio" of doses is greater than one. This ratio is highest, approaching two, for negative pi mesons (Fowler and Perkins, 1961) and for protons (Larsson, 1961; Graffman and Larsson, 1976). The ratio becomes lower (worse) for the doses from helium ions and heavier accelerated particles (Tobias *et al.*, 1971). However, all these particles except protons produce a significant proportion of high LET radiation in the peak with but little in the plateau. Therefore the overlying normal tissues are spared from low LET damage by repair during fractionation, whereas the target volume is spared less because the high LET damage is less repairable.

It is remarkable that pions and heavy particles such as carbon or neon ions have fairly high values of OER, about 1.7, and relatively low values of RBE, similar to fast neutrons. It is likely that neutron beams have slightly lower values of OER than do the peaks from pions when they are spread out to irradiate realistically large target volumes (Raju *et al.*, 1978). British workers using the pion beam at the Rutherford Laboratory have explored these factors with the spread-out pion peaks (Ellis *et al.*, 1976); it is hoped that further work with pions will be possible when the spallation neutron source is in action at the Rutherford Laboratory.

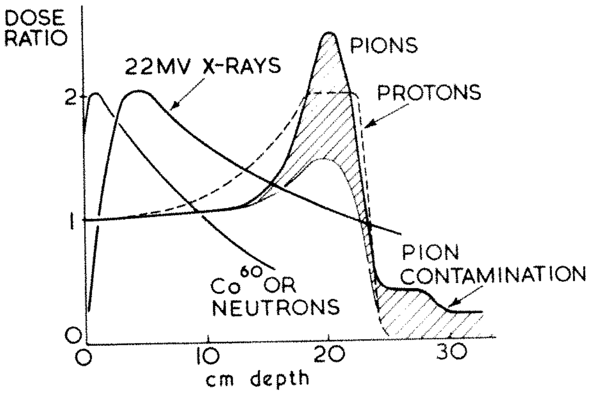

FIG. 4.

Central axis depth doses for different types of radiation beam used in radiotherapy (Fowler, 1976).

Pions are being used to treat patients at Los Alamos (Kligerman *et al.*, 1978). They will be used clinically at Villigen near Zurich and at Vancouver. If their results are good, we shall not know whether it is because of the good physical dose distribution or because of the good radiobiological effects of the high LET component of the beam. Results from proton beam treatments can tell us if it is the physical advantage, because protons have similar depth dose characteristics but do not act as high LET beams. They are being used in Boston and in Moscow at present. Results from better neutron beams will be needed to tell us if the high LET advantage is the important one.

The use of protons (which are radiobiologically low LET particles) to give a good physical distribution, combined with hypoxic-cell radiosensitizers to reduce the OER, is an obvious possibility. This brings in the question of cost. It would cost about £2M to install a neutron-producing cyclotron with reasonable depth dose. It would cost about twice that to install a purpose-built proton therapy machine and twice that again for a heavy charged-particle therapy machine. Pions are even more expensive because they are secondary particles so that adequate dose rates require high-current accelerators.

Hypoxic cell radiosensitizers

The third main method, in historical sequence, of dealing with hypoxic cells arose from fundamental work on the nature of the oxygen effect by Adams and Dewey in 1963. This work has led to the two drugs which are at present of clinical interest metronidazole (Flagyl)* and misonidazole (Ro–07–0582)†. Such drugs sensitize hypoxic cells to X rays because they are electron-affinic, as oxygen is, and will remove any free electrons released when a molecule is ionized. They are not used up in the metabolism of cells, however, so they can diffuse further from blood capillaries than oxygen (Adams, 1977). Misonidazole sensitizes hypoxic cells in culture by a dose-reduction factor of 2.5, *i.e.* almost as large as the full OER of 2.75. In animal experiments, sensitizer enhancement ratios (SER) of about 2 have been obtained in over a dozen types of tumour in mice (Fowler, 1977a and b), using high concentrations of misonidazole. The shaded area in Fig. 5 shows the tumour control rates achieved in mouse tumours *in vivo* for realistic clinical concentrations.

In clinical use the neurological side effects limit the dose to a total of 12 g/m^2 in a three or four week

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*May and Baker Limited, Dagenham, Essex.

†Roche Products Limited, Welwyn Garden City, Herts.

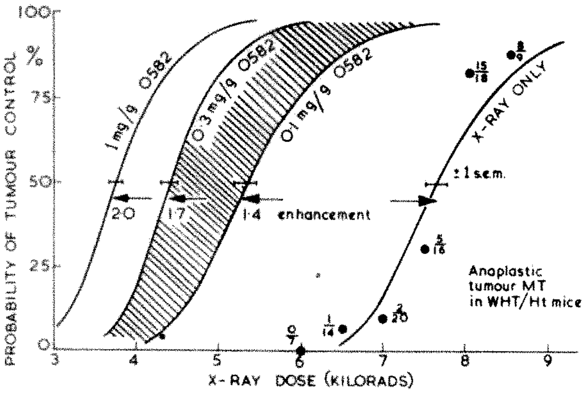

Fig. 5.

Local control of the mouse MT tumour using X rays alone (right-hand curve) and 1 mg/g misonidazole plus X rays (left-hand curve). The shaded area represents results for tumour concentrations achievable in human tumours without prohibitive neurotoxicity (Sheldon and Hill, 1977).

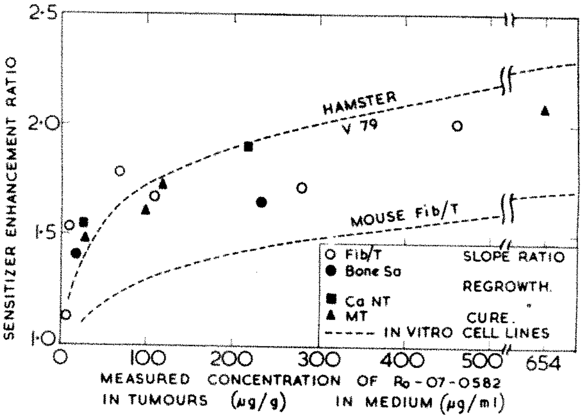

Fig. 6.

Sensitizer enhancement ratio versus measured concentration of misonidazole. Points—four types of solid mouse tumour *in vivo*. Curves—two types of mammalian cells in culture dishes (McNally *et al.*, 1978).

schedule (Dische *et al.*, 1977). This means that concentrations of misonidazole in human tumours of 60–100 μg/ml can be achieved if six big doses are given whereas only 15–25 μg/ml can be obtained if 30 or 20 small daily doses are administered. From animal experiments, where the tumours were irradiated *in vivo*, these concentrations of misonidazole would be expected to yield significant radiosensitization of the hypoxic cells by a factor of about 1.6–1.7 with six fractions and 1.2–1.4 with many small doses (Fig. 6).

I should like to comment on the question of whether it is better to use a few large or many small doses. Although we could obviously obtain a higher enhancement ratio using a few large doses (as with neutrons), the X-ray-only base-line may be so poor that the improvement would only bring the result with sensitizer up to a normal level (an indication of this is seen in the results of the MRC trial of HBO for Ca cervix for those centres using only six fractions, Table II). It therefore seems better to start with a good conventional fractionation schedule and add radiosensitizer, provided there are not so many small doses that the SER predicted for each is less than a detectable difference from unity such as 1.2 (see Fig. 6). In practice, it is reasonable to expect that 20 or even 30 daily fractions of misonidazole, but not metronidazole, should lead to a clinically detectable improvement in results if hypoxic cells are a problem in human tumours.

The single dose values of SER are similar to the hypoxic gain factors achievable with neutrons (Fig. 5). It has been shown that the use of neutrons and misonidazole combined can give better results, in two types of mouse tumour that are not completely reoxygenated, than the use of either neutrons alone or X rays plus misonidazole (Fig. 7; Denekamp *et al.*, 1977). This would be expected from the fact that neither agent alone completely eliminates the problem of hypoxic cells.

Other hypoxic-cell sensitizing drugs are being developed, but it is likely to take several years to find and test alternatives which are significantly better than misonidazole. The clinical use of these sensitizers should demonstrate, better than any other method, whether hypoxic cells matter or not in radiotherapy, since their only authenticated effect is on hypoxic cells, whether by radiosensitizing them or by specific cytotoxicity.

Fractionated X rays, Neutrons and Radiosensitizers

A series of multiple-fraction experiments has been carried out using a C3H mouse mammary tumour which reoxygenates well, in order to assess the relative advantages of fractionated X-ray schedules and other methods of dealing with hypoxic cells (Fowler *et al.*, 1976). A parallel series of fractionated irradiations was carried out on a normal tissue in mice, measured by skin reactions, in order to

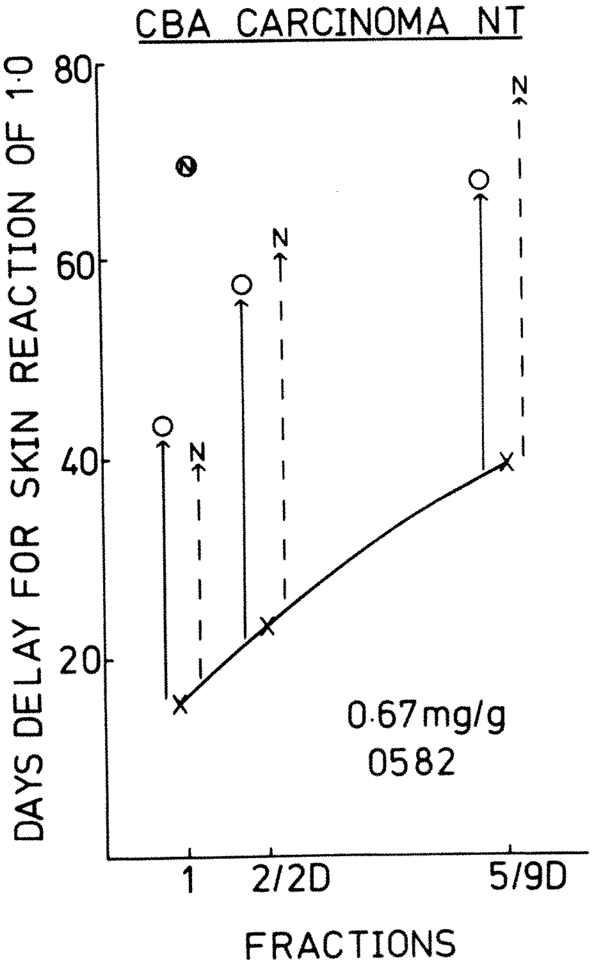

FIG. 7.

Effect on tumour (regrowth delay) for a constant level of acute skin reaction. Crosses—X rays only. N—neutrons only. 0—misonidazole plus X rays. Ⓝ—misonidazole plus neutrons (Denekamp *et al.*, 1977).

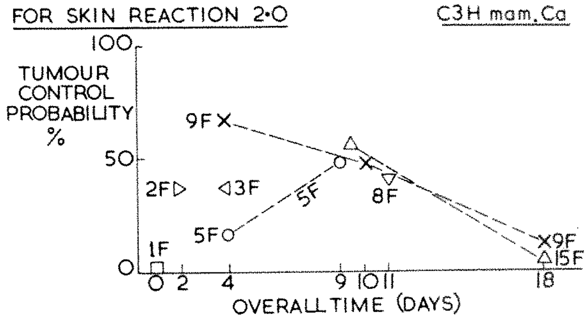

FIG. 8.

X rays only. Tumour control for doses that produce a constan tskin reaction.

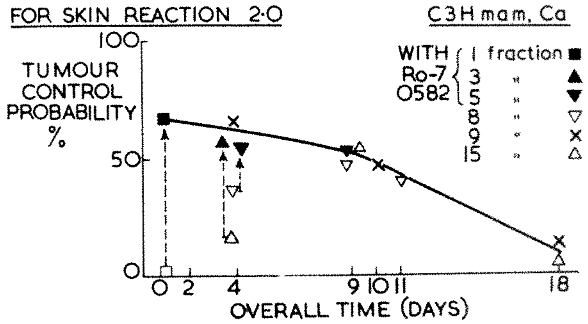

FIG. 9.

X rays plus misonidazole.

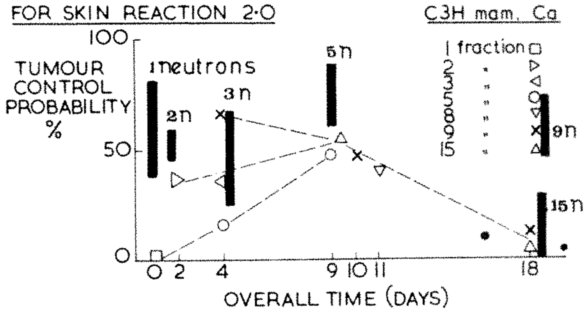

FIG. 10.

Cyclotron neutrons (bars).

have a basis for a comparison of "therapeutic ratios". The results are presented as the percentage of tumours cured in each schedule, for a dose that produced a constant level of acute skin reaction (Figs. 8, 9 and 10).

The results for X rays alone are shown in Fig. 8. The volume doubling time of these tumours averaged about six days, so that days in Fig. 8 might represent weeks in human tumours, assuming that volume doubling time is a reasonable basis of comparison. It is clear that 18 days was too long: the tumours outgrew the treatment. Nine or ten days represented an optimum overall time; the results were all similar and reasonable at 50 to 60% cure probability. At shorter overall times there was enormous variability. This was explainable by poor reoxygenation for daily intervals (5F/4d) but better reoxygenation for two-day intervals (3F/4d), especially if a reasonable time was allowed for tumour shrinkage and reoxygenation (5F/9d) (Denekamp, 1977; Dische *et al.*, 1979). Thus X rays alone could produce good results in this well-reoxygenating tumour, but not if the overall time was too short to allow reoxygenation, nor too long so that tumour cell proliferation became important. The relevant kinetic parameters are not known for any human tumours.

How much did misonidazole help? Figure 9 shows the results. Single dose results were much improved, as were those for the poor 5F/4d schedule. The mediocre 3F/4d was improved to the same level as the others and the previously good 5F/9d schedule hardly at all. The striking result is that there are no longer any poor schedules at short overall times. The hypoxic-cell radiosensitizer has taken the variability out of the schedules, provided they are not too extended.

This seems to me one of the most important contributions to radiotherapy that these radiosensitizers might make. If, by overcoming hypoxic radioresistance, they make possible successful schedules using shorter overall times than before, the consequences in terms of time and cost for patients, the shortening of waiting lists and hence reduced chance of spread, not to mention bed occupancy and time spent by staff and radiotherapy equipment, would be very great.

In principle the same advantage—shorter overall times—may apply to neutron therapy or to superfractionation too, although further radiobiological experiments are required to demonstrate it. Figure 10 shows the corresponding results for neutrons alone, as compared with X rays alone. The same trend towards uniformly good schedules is shown, especially at short times, but fewer experiments have been done than with hypoxic-cell radiosensitizers.

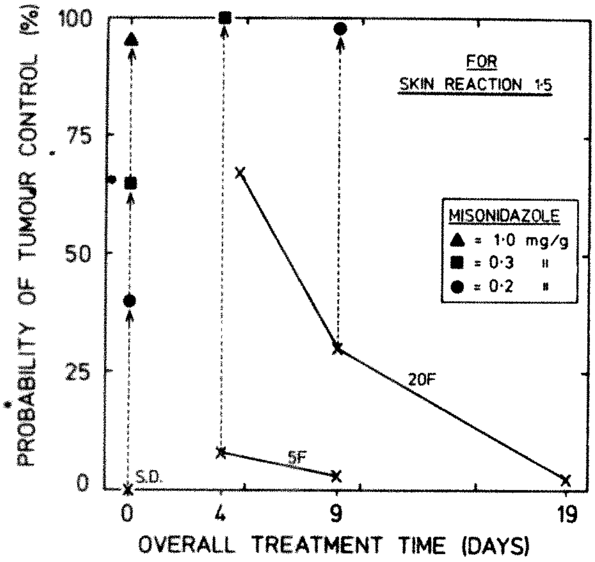

Fig. 11.

As Figs 8, 9 and 10 but for the poorly reoxygenating MT tumour in WHT/H$_1$ mice (Sheldon and Fowler, 1978). Skin reaction doses calculated in an arbitrary way.

Figure 9 showed an example of hypoxic-cell radiosensitizers bringing poor fractionation schedules up to the same level as good schedules. Figure 11 shows results for a different type of murine tumour. The crosses and full lines show results for X-rays alone. The volume doubling time was little more than one day, so short schedules were best. The dotted lines and solid symbols show the improvement in tumour response when misonidazole was used. The important point is that even the poor schedules were then improved to yield a better response than the best of the schedules tested with X rays alone. This is because the tumours were only slowly reoxygenating, in contrast to the C3H mouse tumours which shrank and reoxygenated readily. It is not known whether most human tumours are poorly reoxygenating like those in Fig. 11, or readily reoxygenating like those in Fig. 9.

Hyperthermia

It has been suspected for over a century that tumours sometimes regress in patients with a fever. Recently a new wave of research interest has begun, based on quantitative laboratory measurements. Clinical work has also gone ahead, before there is a sound biological basis for it, as has happened many times in the treatment of cancer.

There is general agreement that a moderate degree of hyperthermia will decrease the tolerance of normal tissues to damage by ionizing radiation. In many laboratory experiments on rats and mice this sensitization of normal tissues by heat is a large factor: the X-ray dose must be halved if tissues are exposed to 42–43°C for one hour at about the same time as irradiation (Field, 1978; Stewart and Denekamp, 1977). In other laboratories and in larger animals the sensitization is reported to be somewhat less.

In our laboratory there is no systematic difference between the thermal sensitization to X rays of mouse tumours and normal tissues if the heat is applied immediately before or after the X-ray dose. If, however, X radiation is given first, followed by a gap of three to six hours before heating (42°C/1 hr), then almost all the enhancement of radiation damage has disappeared in normal tissues but not in tumours (Stewart and Denekamp, 1978; Hill and Denekamp, 1979). This suggests an obvious way of obtaining a therapeutic advantage but further research is required. When multiple fractions of heat are used a phenomenon known as "thermal tolerance" or "heat-induced resistance" occurs so that subsequent exposures to heat appear not to have such a large effect as the first one. This too requires further research as does the subject of late injury relative to early injury after heat and the question of whether hyperthermia increases metastatic spread. The use of modest hyperthermia can also enhance the effectiveness of the direct cytotoxicity of hypoxic-cell radiosensitizers (Stratford and Adams, 1977; Bleehen *et al.*, 1977) and of other chemotherapeutic drugs (Hahn, 1978).

Hypethermia seems to me to be in the same state as radiotherapy in the 1920s. There are no good ways of delivering the heat. Measurement is crude and concepts of "heat dose" (time in minutes multiplied by degrees above 40°C, for example) are still being worked out. Much remains to be done by physicists on these aspects. Biological results from different laboratories can differ. The processes of repair and thermal tolerance need much further study. But the research field is an active one and the results may influence the strategy of radiotherapy within a few years.

Combinations of Radiotherapy and Chemotherapy

Chemotherapeutic drugs cannot usually be restricted to limited regions of the body, and not all cells in solid tumours may be accessible to cytotoxic drugs. Nevertheless rational combinations of various cytotoxic drugs with well-localized ionizing radiation and/or fairly well localized heat is a logical development. It is in dealing with metastatic cancer that the biggest gains can be expected from chemotherapy. The primary tumour must also be sterilized completely or it will regrow and reseed metastases. The successful treatment of primary tumours will become even more important when chemotherapy or other methods can deal more successfully with widespread metastases. The example of Hodgkin's disease mentioned above is a good one. It is in the field of combinations of various modes of therapy that we can expect the biggest gains in future cancer treatment.

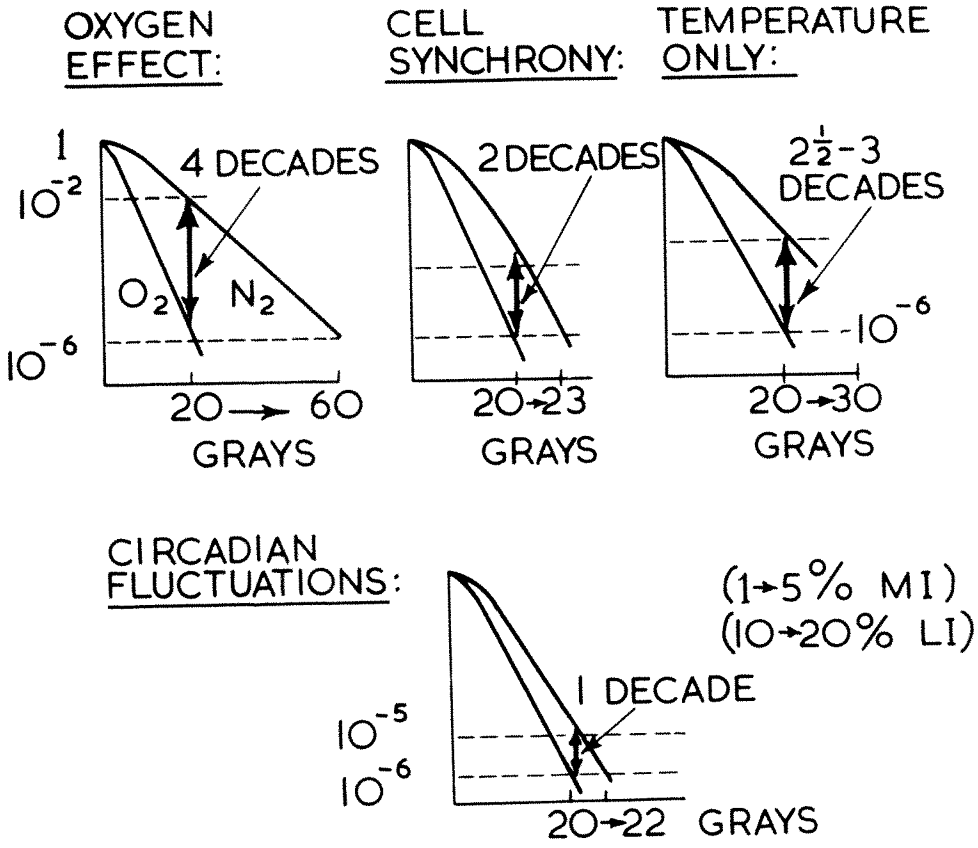

Fig. 12.

Estimates of the gain in cell kill in cancer treatment using various modalities.

Conclusions

Figure 12 summarizes the expected magnitude of various possible ways of improving the "cell kill" in cancer therapy (Fowler, 1978a). The elimination of hypoxic cells appears to be the largest effect, followed by hyperthermia. Circadian fluctuations or chemotherapy could of course be used together with any of the other methods.

Improvements in radiotherapy alone and in combination with the other methods described are taking place at least as rapidly as they can be demonstrated by clinical trials. Further improvements in cure rates and more widespread education about the curability of cancer would lead to earlier submission of patients; such a change in the pattern of referral would in itself help the process of gradual improvement in the treatment of cancer. The submission of earlier cases demands, in turn, better methods of diagnosis and treatment so that progress in cancer research and treatment should continue to be a rising spiral.

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Selective angiography in renal and peri-renal inflammatory lesions: correlation with histopathology

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ABSTRACT

We have correlated the angiographic and pathological findings in renal and peri-renal inflammatory disease in acute, sub-acute and chronic phases. In all stages of renal infection, the renal vasculature is attenuated. This corresponds in acute inflammation to vasospasm, acute vascular necrosis and post glomerular peritubular capillary congestion. In sub-acute inflammation, the reduction in vascularity is due to peri-vascular fibrosis and intimal and medial hyperplasia. In chronic infections, the renal vessels are completely destroyed and replaced by fibrotic tissue. In contrast to this, peri-renal inflammatory disease leads to vaso-dilatation and enlargement of the renal capsular arterial complex, and of retroperitoneal arteries.

If both renal and peri-renal inflammation occurs simultaneously, a discordance between the renal cortical and capsular arterial filling results: this striking phenomenon is highly suggestive of inflammation, and extremely rare in tumours. Three types of inflammatory vascularity are described, two of which can be easily distinguished from tumour vascularity. An inflammatory blush, slow emptying of vessels and a mottled nephrogram with loss of cortical definition are highly suggestive signs of renal inflammation. It is concluded that angiography is a sensitive and accurate method for the early diagnoses of renal and peri-renal inflammatory conditions.

Inflammation of the renal and peri-renal space represents an unusually difficult and frustrating diagnostic problem for clinicians and radiologists alike. Diagnosis may be delayed, with resultant prolonged morbidity and high mortality (Thorley *et al.*, 1974). Frequently the only therapeutic option is to resect an irreversibly damaged, non-functioning kidney. Early and accurate diagnosis and immediate institution of intensive parenteral antibiotic therapy, on the other hand, can result in complete morphological and functional recovery of the organ.

TABLE I

ANGIOGRAPHIC FINDINGS IN 44 SELECTIVE RENAL ARTERIOGRAMS IN CASES OF RENAL AND PERI-RENAL INFLAMMATION

	No.	%*	Diagnostic significance‡ in differentiation from neoplasm
Arterial phase			
(1) Attenuation or amputation of arcuate and interlobar arteries	42	95	++
(2) Enlargement of capsular arteries	16	36	+
(3) Simultaneous occurrence of (1) and (2) (cortical-capsular arterial discordance)	16	36	++
(4) Attenuation of segmental and interlobar arteries	29	66	++
(5) Stretching and displacement of segmental and interlobar arteries	29	66	+
(6) Attenuation of the main renal artery	10	45†	++
(7) Capsular artery displacement	18	41	+
(8) Inflammatory vascularity	20	45	++
(9) Slow flow	23	52	++
(10) Tumour vascularity	0	0	
Parenchymal phase			
(1) Delayed nephrogram	23	52	++
(2) Mottled nephrogram	38	86	++
(3) Loss of cortical definition	38	86	++
(4) Early venous filling	0	0	
(5) Inflammatory stain	6	14	++

*Rounded to full numbers.

†Based on 22 cases. Excluded are those with multiple renal arteries, bilateral disease or inadequate midstream aortograms.

‡ + low significance.

++ high significance.

+++ diagnostic.

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TABLE II

ANGIOGRAPHIC–HISTOLOGIC CORRELATION IN RENAL AND PERI-RENAL INFLAMMATION

Histologic stage of inflammation	Angiographic findings	Histologic correlate	Pathophysiologic correlate
Acute	*Arterial phase*: attenuation of usually small cortical arteries, occasionally extending to the main renal artery, reversible in some areas with papaverine hydrochloride. Moderate dilatation of capsular, peripelvic, periureteric and retroperitoneal arteries. *Parenchymal phase*: delayed, protracted, pale, mottled nephrogram, loss of cortical definition. Inflammatory stain.	Acute vascular necrosis, postglomerular-peritubular capillary congestion with neutrophils. Moderately enlarged capsular arteries. *De novo* formed inflammatory arterioles + capillaries.	Vasospasm
Subacute	*Arterial phase*: Attenuation and mild to moderate tortuosity of small and medium sized arteries, not reversible with papaverine hydrochloride. Progressive enlargement of the capsular arterial complex. *Parenchymal phase*: (same as above.)	Intimal and medial hyperplasia, perivascular fibrosis, enlarged and increased number of capsular arteries. *De novo* formed inflammatory arterioles and capillaries.	
Chronic	*Arterial phase:* attenuation and amputation of arteries of all sizes. In extreme cases complete obliteration of the main renal artery. Large capsular arterial complex. *Parenchymal phase:* (same as above.)	Fibrotic encasement and destruction of parenchymal arteries. Capsular artery enlargement. *De novo* formed inflammatory arterioles and capillaries.	

Excretory urography, radionuclide studies, sonography and computerized axial tomography, singly or in various combinations, at best allow one to establish unequivocally the presence or absence of a clinically suspected renal or peri-renal mass. Uncertainty frequently persists as to whether this mass is neoplastic or inflammatory in nature. The inflammatory process may be diffuse without mass effect. In our experience selective renal angiography, though not infallible, is an exquisitely sensitive tool for diagnosis of renal and peri-renal inflammatory processes. We report here our experience with 44 proven cases and describe a new angiographic sign. The angiographic findings are correlated with histopathologic changes in an attempt to broaden our understanding of the subject and to facilitate diagnosis.

MATERIALS AND METHODS

Case material from 1969 to the present was selected from our files on the basis of two criteria. First, the diagnosis of renal and/or peri-renal inflammation had been confirmed. Confirmation was reached by nephrectomy in 20 cases, incision and drainage of an abscess in 11 cases, surgical exploration and biopsy in six cases, positive urine culture and clinical and radiographic response to antibiotics in four cases, and drainage of an obstructed pyohydronephrotic kidney through a stent in one case. Second, serial angiograms of adequate radiographic quality had to be available for review. Forty-two cases involving 44 infected kidneys fulfilled these prerequisites. Two patients had arteriographic follow-up six weeks and 12 months after the initial arteriogram respectively. The last eight patients in addition to selective arteriography had a second selective arteriogram which was enhanced by intra-arterial injection of 30 mg of papaverine hydrochloride 90 seconds before contrast injection. Angiograms obtained from 1969 to June 1974 were jointly reviewed by the radiologists with full knowledge of the pathologic diagnosis. Twenty-one examinations performed during the course of this study were diagnosed prospectively.

Most of the described angiographic signs are self-explanatory; however, a few need clarification:

Slow flow: a dynamic change manifested as contrast persistence in arteries of the affected area while

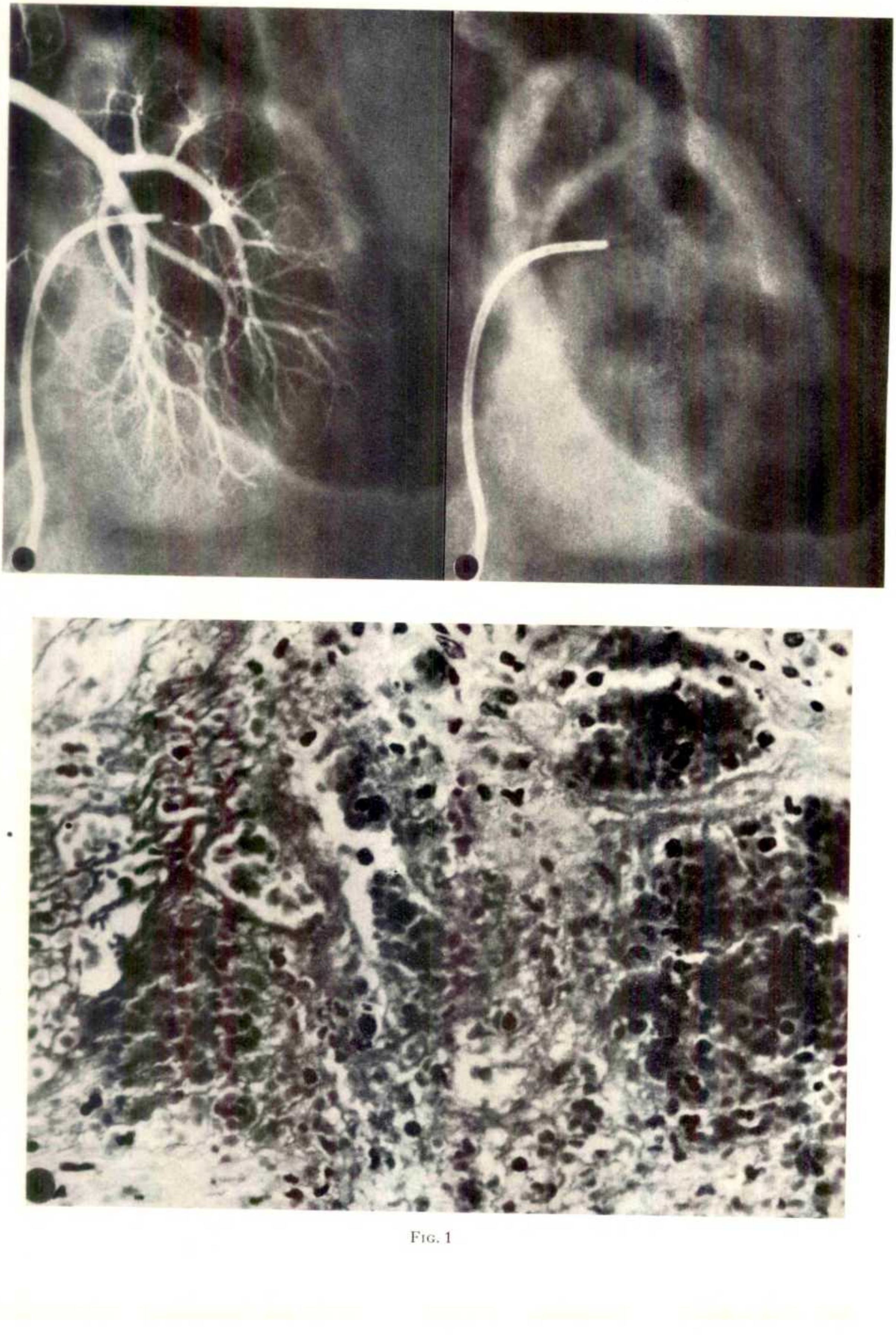

FIG. 1

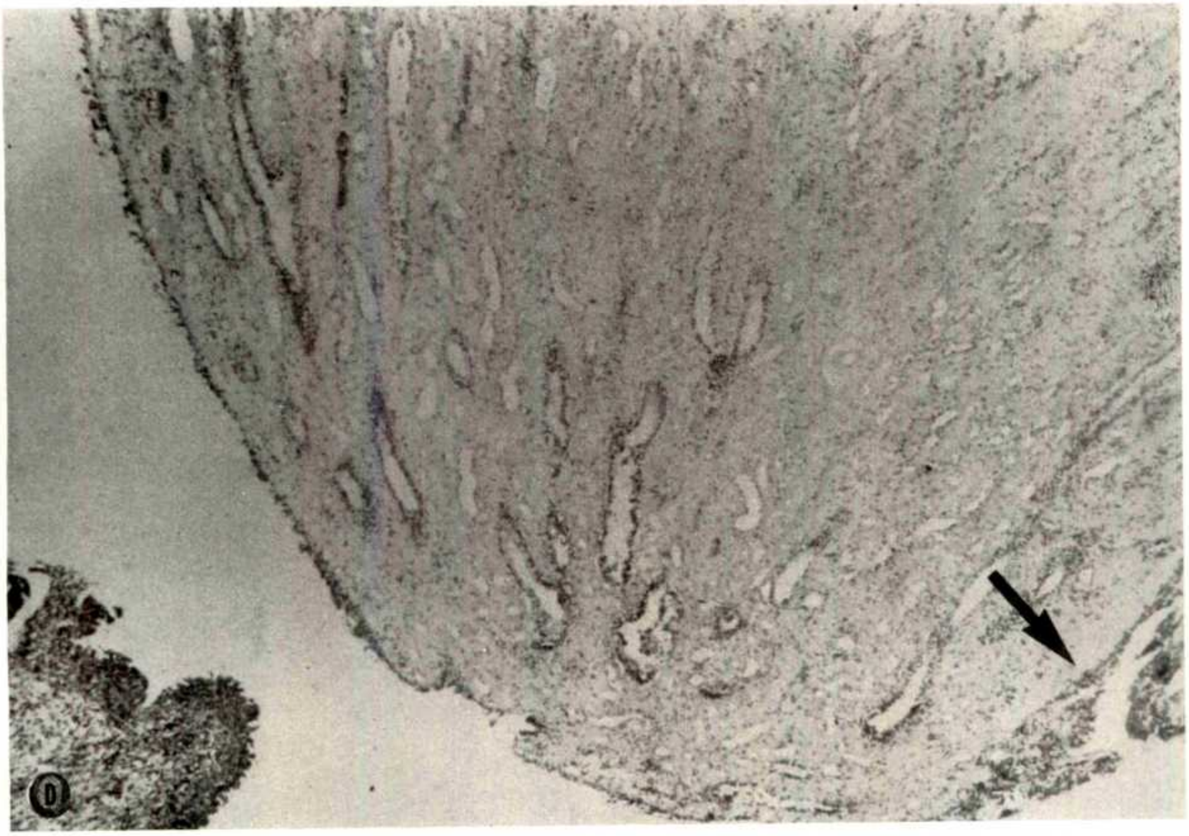

FIG. 1.

Clinically acute renal infection. 53-year-old diabetic white female with acute flank pain and fever. Urine culture grew E. coli. (A) 1.5 seconds after contrast injection distal arcuate arteries of the lower pole are attenuated and the cortex is indistinct. The capsular and peripelvic artery in the lower pole is moderately enlarged.
(B) The cortex of the lower pole is pale and indistinct.
(C) Acute vascular necrosis with haemorrhage. (H. & E, 4000 ×)
(D) Beginning acute papillary necrosis (arrow). (H & E, 100 ×)

unaffected renal parenchyma exhibits the nephrographic phase.

Tumour vascularity: vessels of irregular course and calibre with marked luminal variations over short distances and often exhibiting arteriovenous shunts and venous puddling.

Delayed nephrogram: lagging or absence of parenchymal staining compared with normal parenchyma.

Loss of cortical definition: disappearance of the normally distinct renal outline and/or the corticomedullary junction in the nephrographic phase.

Tissue available from nephrectomy in 20 cases was cut in areas identified from the angiogram, stained with haematoxilyn-eosin and van Gieson and examined microscopically by one of us (B.M.K.). Histologic and angiographic findings were subsequently correlated.

RESULTS

The angiographic findings are summarized and their diagnostic significance in the differentiation from neoplasm and other non-inflammatory conditions indicated in Table I. Table II correlates angiographic, histologic and pathophysiologic findings.

One of the arteriographic hallmarks of renal parenchymal inflammation is attenuation of the renal vasculature. In acute inflammation attenuation is usually limited to small areas in the cortex (Figs. 1A, 2A, 5A) but can extend to include even the main renal artery (Fig. 3A). In more advanced cases larger segmental and interlobar arteries may be involved (Figs. 6A, 8A, 9A). Finally, in long standing extensive lesions the main renal artery itself may be completely obliterated (Fig. 13A). We found attenuation in

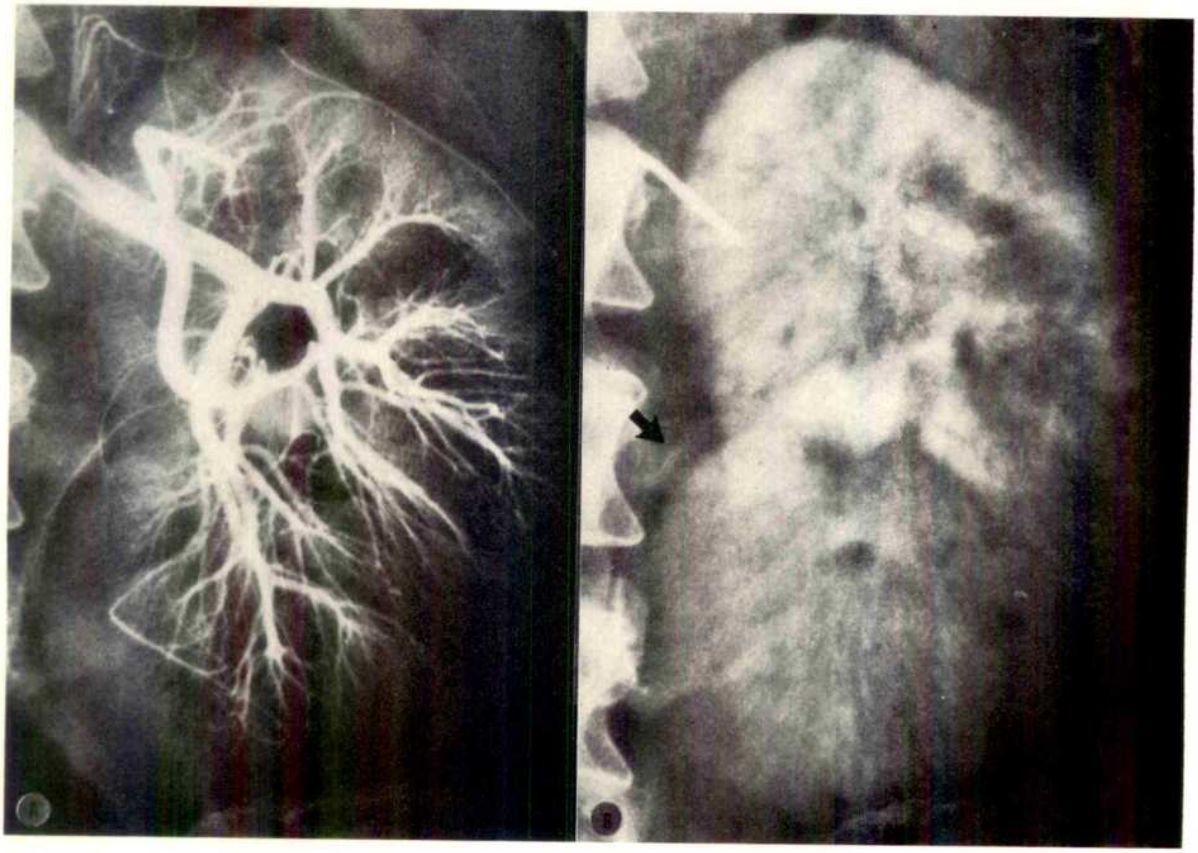

FIG. 2.

Clinically acute renal infection. Forty-two-year-old white male with a one week history of chills, dysuria and bilateral flank pain. Blood and urine cultures grew E. coli.

(A) Two seconds after contrast injection arcuate arteries in the lower pole are markedly attenuated. There is no cortical staining except in the upper pole. The capsular arterial complex in the upper and lower medial pole are moderately attenuated and show branching

(B) The nephrogram of the lower pole is streaky with loss of cortical definition. An inflammatory blush is seen in the region of the pelvis (arrow). The patient responded clinically to ampicillin therapy. One month later a repeat sonogram revealed complete resolution of earlier sonolucent parenchymal defects.

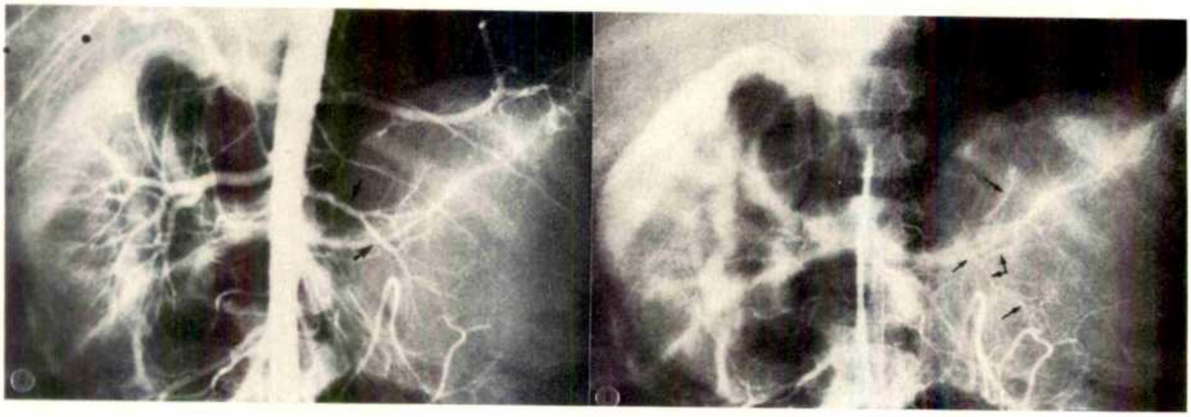

FIG. 3.

Clinically acute renal infection. Two-year-old girl two weeks after sustaining multiple blunt trauma to head, chest and abdomen. After an initial abdominal exploration and closure of multiple bowel perforations, she spiked a fever of 103°F.

(A) Marked attenuation of the renal artery and all peripheral branches. No capsular arteries are seen.

(B) Eight seconds after contrast injection some renal arteries are still filled with contrast (arrows). There is essentially no neophrogram. A perinephric abscess was drained from which E. coli was cultured.

virtually all infected kidneys in this study. Two cases did not show this phenomenon. In both the inflammatory process did not involve the renal parenchyma but was confined in one to a peripheral renal cyst and in the second to the perinephric and retroperitoneal space. The histologic correlate of arterial attenuation varies with the chronicity of the inflammatory process: in acute inflammation, characterized histologically by an exclusively neutrophilic leucocytic infiltrate, we found two vascular changes responsible. One is acute vascular necrosis (Fig. 1C). (Simultaneously we often found papillary necrosis which cannot be identified by clinical imaging procedures at this stage (Figs. 1E, 5E). The other was postglomerular peritubular capillary congestion with neutrophils (Fig. 7C).

Some arteries that were attenuated angiographically demonstrated a normal calibre on histologic examination. They were uniformly associated with acute inflammatory infiltrates. We attribute this apparent discrepancy to spasm which ceases with nephrectomy. The aetiologic role of spasm for some arterial attenuation in acute inflammation was further corroborated through the intra-arterial application of a vasodilator: upon injection of 30 mg of papaverine hydrochloride arterial attenuation could be reversed in some vessels of all eight kidneys examined in this fashion (Fig. 5B).

We found this vasoconstrictive response to infection to be unique to the renal circulation. It can involve all vessels including the main renal artery (Fig. 3A). The renal capsular arterial complex and retroperitoneal arteries, when visualized, responded uniformly with vasodilatation rather than constriction (Figs. 1A, 2A, 4A, 5A, 7A, 8A, 11A).

In subacute inflammation characterized histologically by plasma cell and beginning lymphocytic infiltrate, the attenution is due to intimal and medial

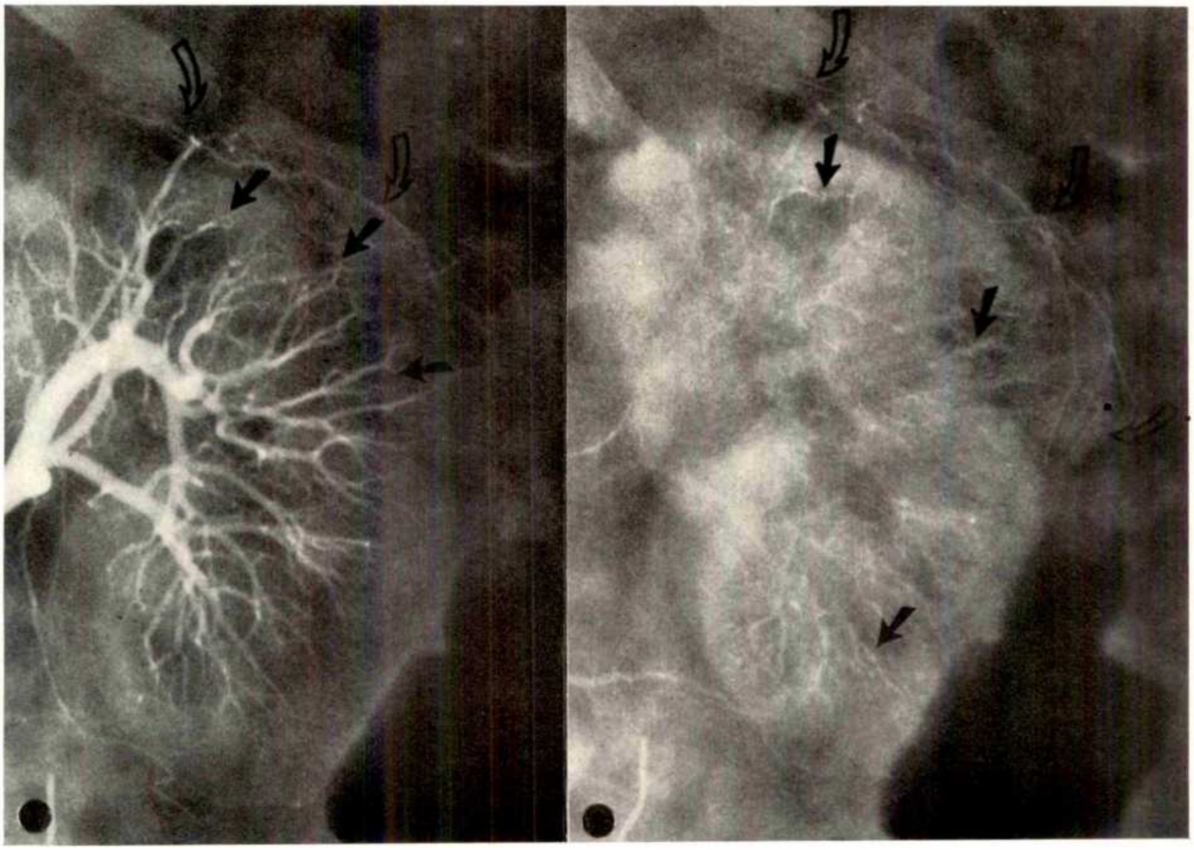

FIG. 4.

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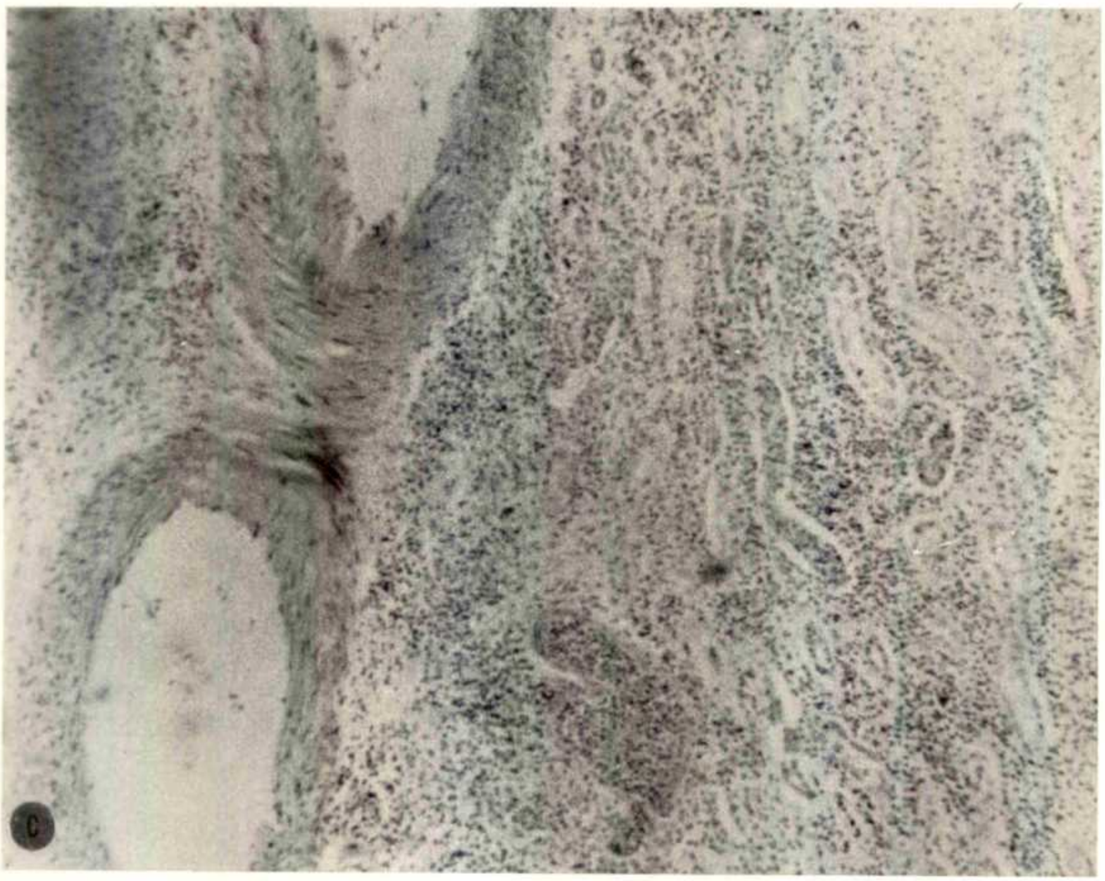


FIG. 4.

Clinically subacute renal infection. Sixty-five year old black diabetic female, disorientated but in no acute distress. Fever of 103.6°F and white blood count of 22 000.

(A) There is no arterial filling distal to the midarcuate level throughout the kidney. Some arcuate arteries are amputated (solid arrows). The capsular arterial complex, peripelvic and ureteric arteries are markedly enlarged and numerous (open arrows).

(B) Six seconds later interlobar and arcuate arteries are still filled with contrast. The nephrogram is mottled with loss of cortical definition.

(C) Distal arcuate arteries are of normal calibre and morphology indicating spasm as cause of their attenuation *in vivo*. (H & E, 2500×)

proliferation with narrowing of the vascular lumen and beginning perivascular fibrosis (Fig. 8C).

In chronic inflammation which is characterized histologically by lymphocytic infiltrate and fibrotic replacement of renal parenchyma, the vascular attenuation is due to fibrotic encasement leading to complete obliteration of the vascular lumen (Fig. 7D). If the infectious process leads to complete destruction of all functioning renal tissue the renal artery itself will be completely obliterated (Fig. 13A).

With progression of the inflammatory process into Gerota's fascia, capsular arterial enlargement results. In early stages the enlargement is moderate (Figs. 1A, 2A, 5A). As the peri-renal inflammation progresses the capsular arteries assume larger sizes and may become more numerous and tortuous (Figs. 4A, 7A, 8A, 11A). In end stages, when the entire renal parenchyma has been destroyed by the inflammation, the capsular artery may be the only remaining blood supply (Fig. 13A and B).

During our examination of inflammatory vascularity, we came to the conclusion that three types have to be distinguished: (A) capillaries and arterioles formed *de novo* in response to inflammation. These

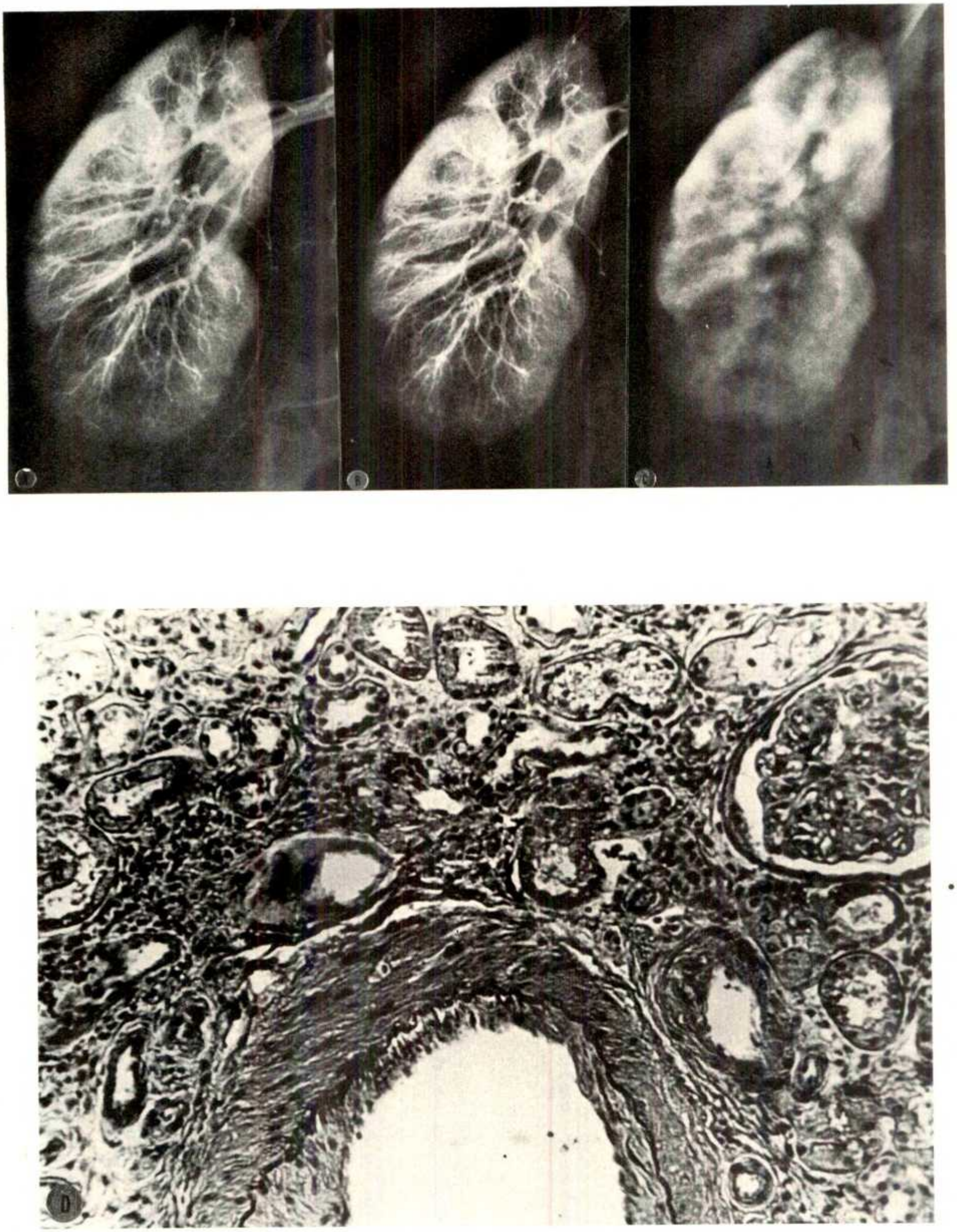


FIG. 5.

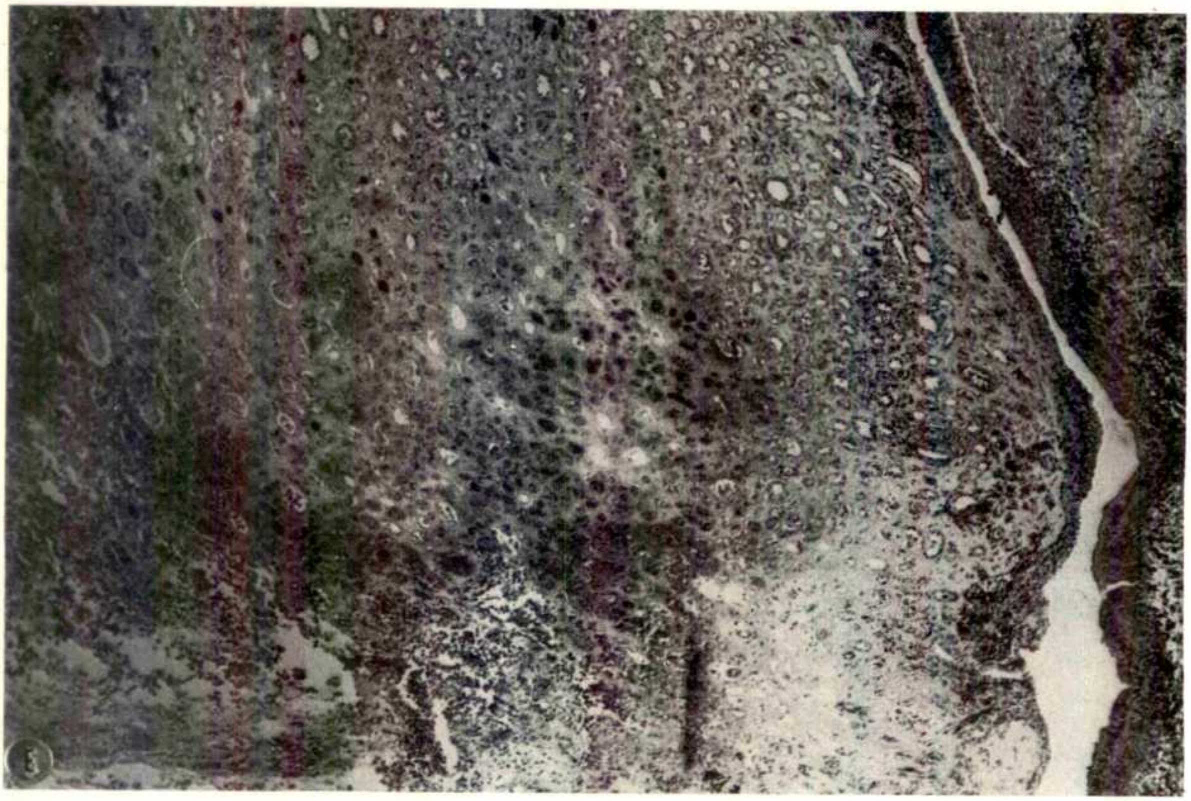


FIG. 5.

Clinically subacute renal infection. Thirty-six-year-old white female with juvenile onset diabetes, had an episode of fever to 102°F, chills, vomiting and diarrhoea two weeks earlier. Blood and urine cultures grew Klebsiella.

(A) Two seconds after contrast injection all arcuate arteries in the lower pole are attenuated. The capsular artery is moderately enlarged and branches frequently.

(B) Repeat study enhanced with 30 mg of papaverine hydrochloride: reversal of the attenuation in some arcuate vessels indicating the spastic nature of this phenomenon.

(C) The nephrogram of the lower pole is pale. A faint inflammatory blush is seen in Gerota's fascia (arrows).

(D) An arcuate artery from the lower pole is of normal calibre but surrounded by inflammatory cells, indicating spasm as cause for *in vivo* attenuation. (H & E, 1000×)

(E) Acute papillary necrosis of a lower pole papilla. Nephrectomy revealed chronic pyelonephritis and acute inflammation in the lower pole. (H & E, 250×)

vessels are too small to be seen in the arterial phase of clinical angiography but can be seen microscopically (Fig. 9D). These vessels reveal their presence in the late parenchymal phase as a dense inflammatory blush in all clinical stages of the disease (Figs. 2B, 5B, 6B, 7B, 8B, 9B); (B) pre-existing vessels enlarged in response to inflammation. These include the renal capsular complex (Figs. 2A, 4A, 5A, 7A, 8A, 11A), pelvic and periureteric vessels (Figs. 2A, 4A, 10A) and retroperitoneal vessels (Fig. 11C). These vessels taper and branch normally. Their abnormality consists in their increased size and their occurrence in unusual locations. They disappear with healing of the inflammatory process (Fig. 10C and D) and are easily distinguished from tumour vessels; (C) pre-existing vessels severely altered in their course and calibre through the influence of inflammation. These vessels occur in the region of the renal pelvis in pyohydronephrosis (Fig. 12). We found these vessels to be difficult to distinguish angiographically from tumour vascularity. Histologically they exhibit various degrees of intimal thickening and luminal compromise and perivascular fibrosis.

The parenchymal phase is characterized by three distinct changes: (1) contrast persistence in arteries of the involved areas (Fig. 3A, 4A, 7A, 10A, 11A). (2)

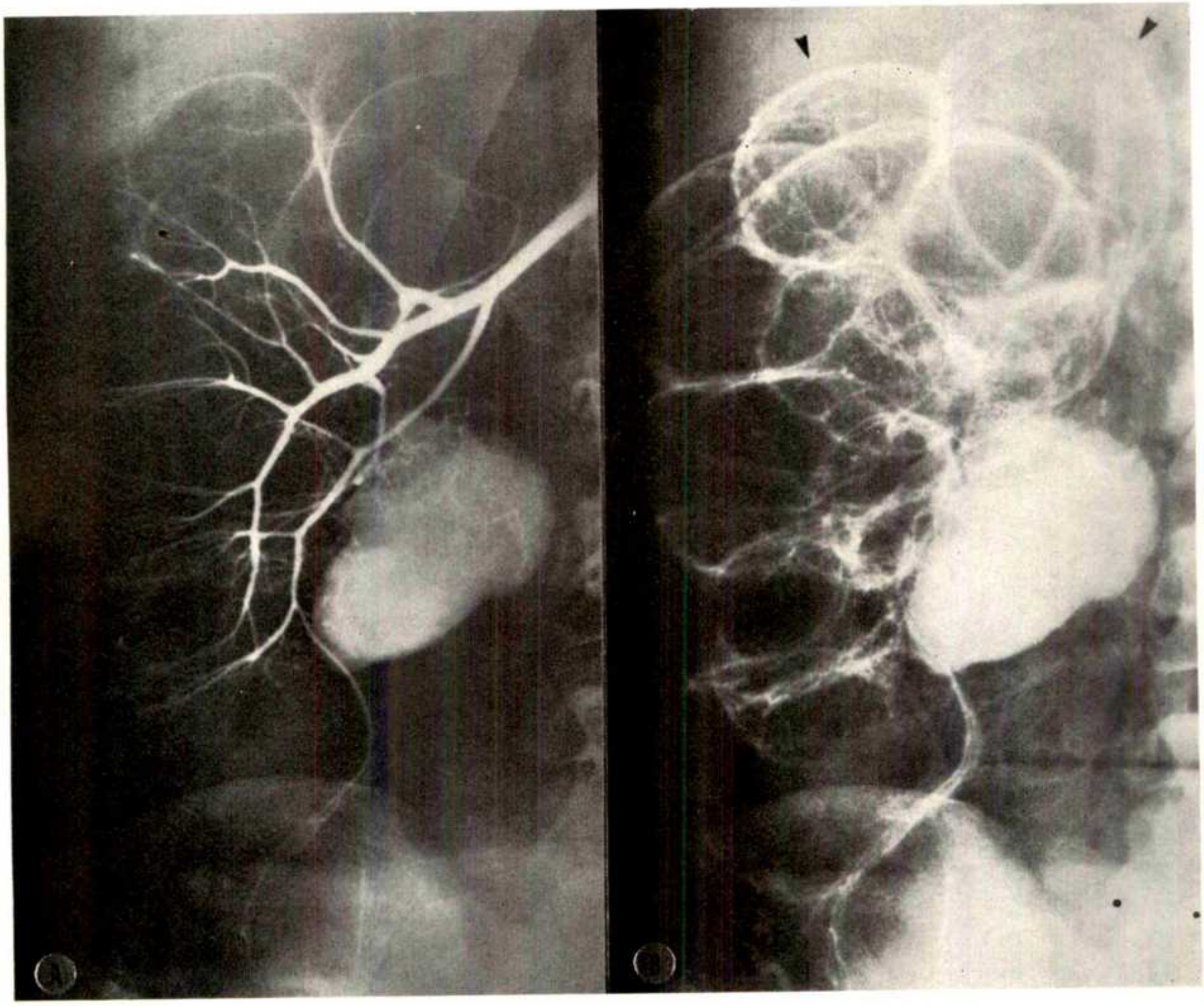


FIG. 6.

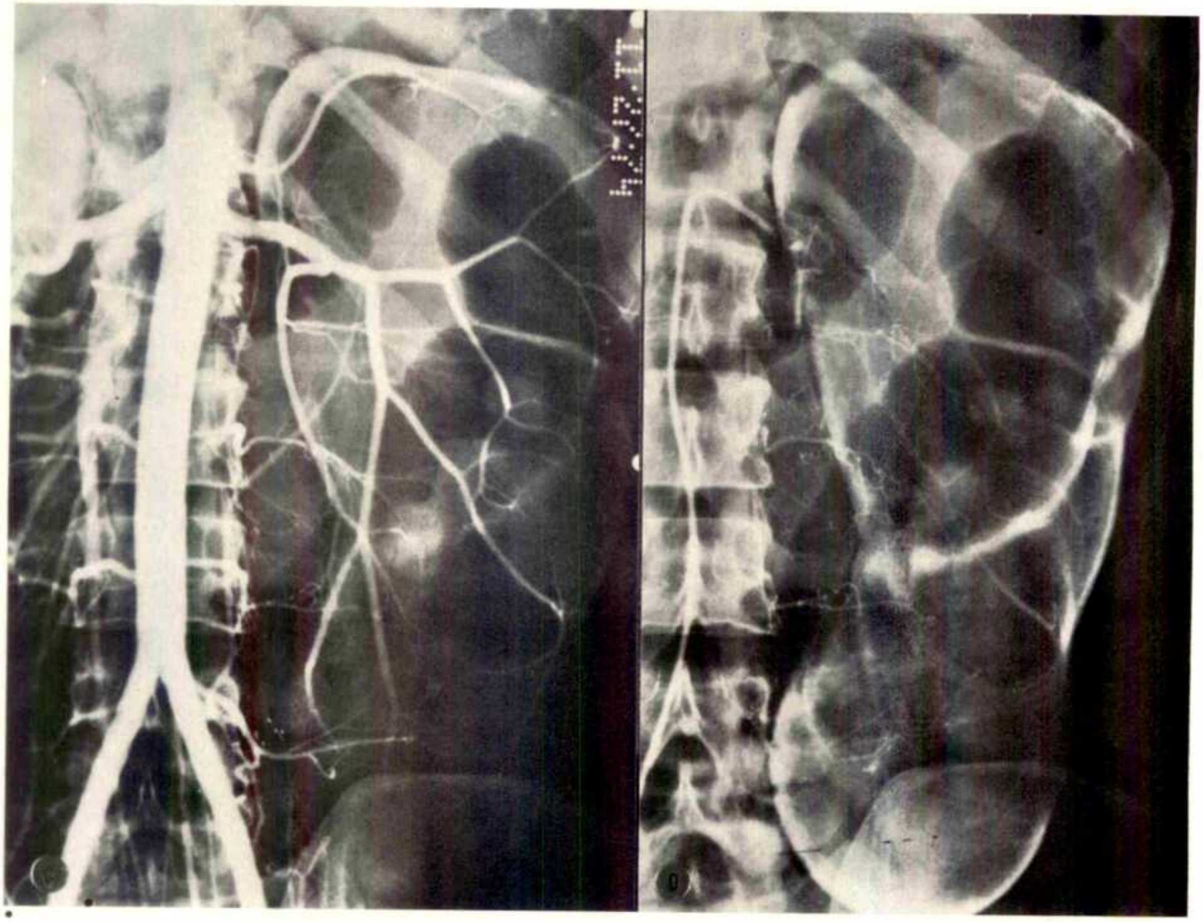


FIG. 6.

Clinically chronic renal infection. Sixty-two-year-old white female with a one year history of abdominal mass and a three to four months history of lower urinary tract irritative symptoms. Excretory urography revealed a right staghorn calculus and a nonfunctioning kidney. Urine culture grew Proteus species.

(A) Marked attenuation of the main renal artery. Splaying and attenuation of segmental, interlobar and arcuate arteries. Staghorn calculus.

(B) Inflammatory blush surrounding lucent areas indicates pyonephrosis.

(C) and (D) In contrast in another patient with non-infected hydronephrosis: the arteries are of essentially normal calibre and no inflammatory blush is seen in the parenchymal phase. At nephrectomy advanced pyonephrosis was found.

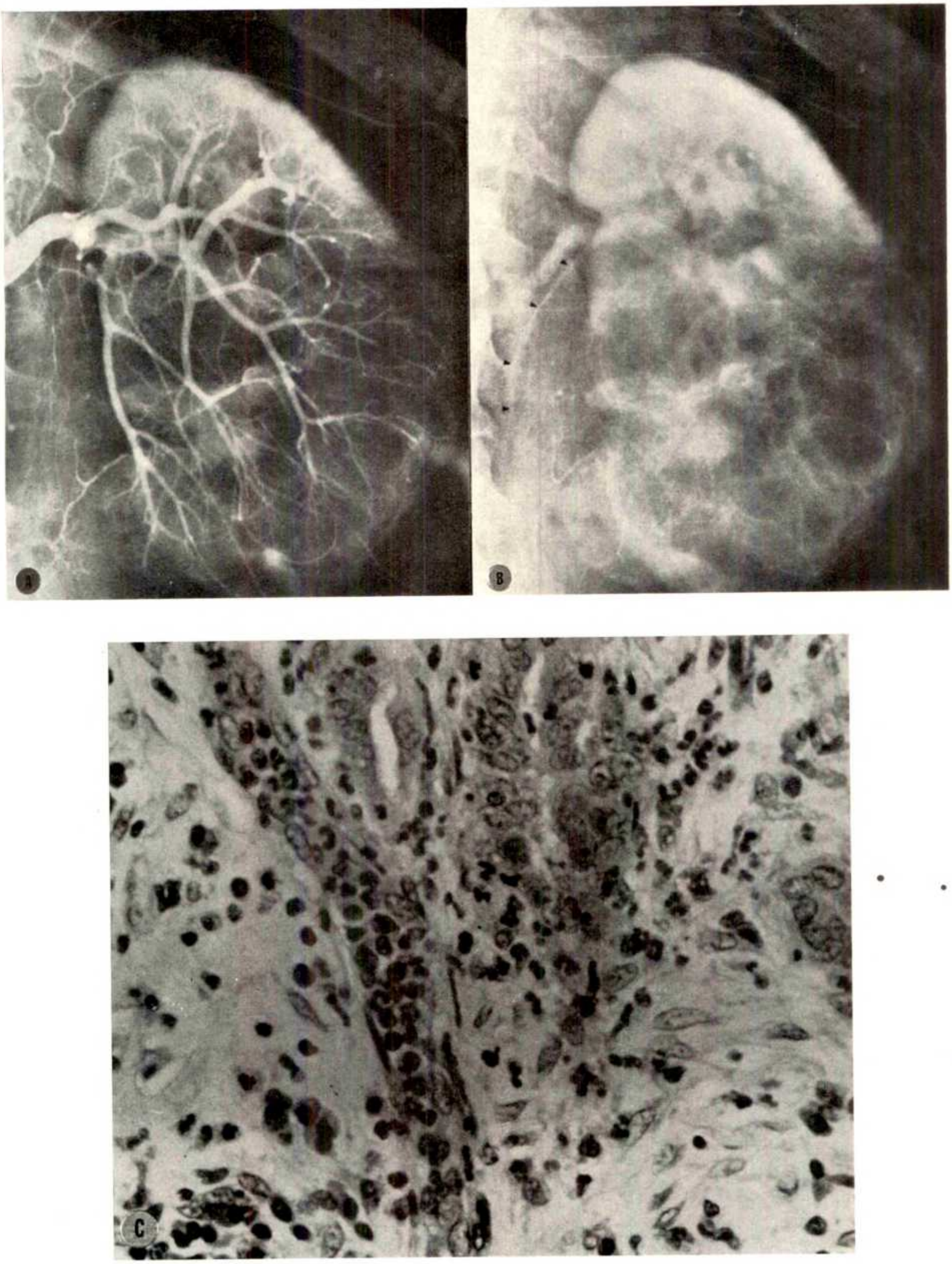


FIG. 7.

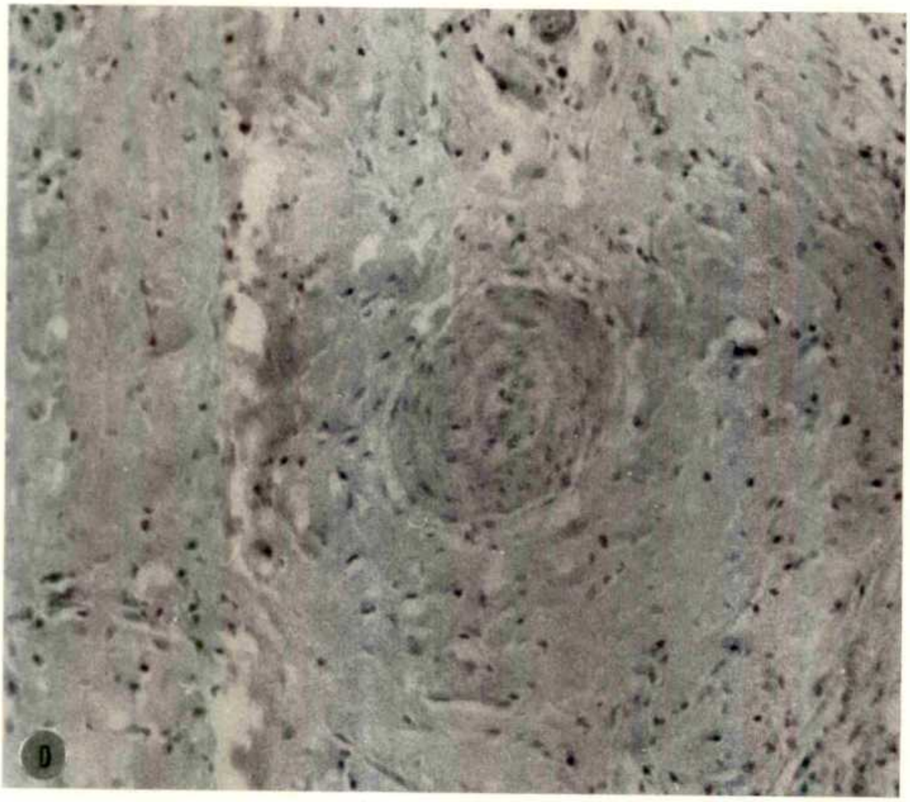


FIG. 7.

Clinically acute and chronic renal infection. Fifty-nine-year-old white female with long history of repeated urinary tract infection and an acute episode of haematuria and pyuria.

(A) Attenuation and stretching of segmental, interlobar and arcuate arteries in the lower two-thirds of the kidney. Capsular and peripelvic arteries are enlarged, tortuous, displaced and branch frequently.

(B) Ten seconds after contrast injection there is persistent arterial filling. The nephrogram is pale, inhomogeneous with several areas of inflammatory stain surrounding lucent areas. A particularly dense staining inflammatory blush stains the abscess wall in the pelvic area (arrows).

(C) Peritubular postglomerular capillary congested with neutrophils are seen in acutely inflammed tissue (H & E, 4000 ×).

(D) Perivascular fibrosis in chronically infected areas completely occluding the vascular lumen. At nephrectomy a perinephric abscess and six well circumscribed renal cystic cavities containing pus, haemorrhagic and necrotic material were found. (H & E, 2500 ×)

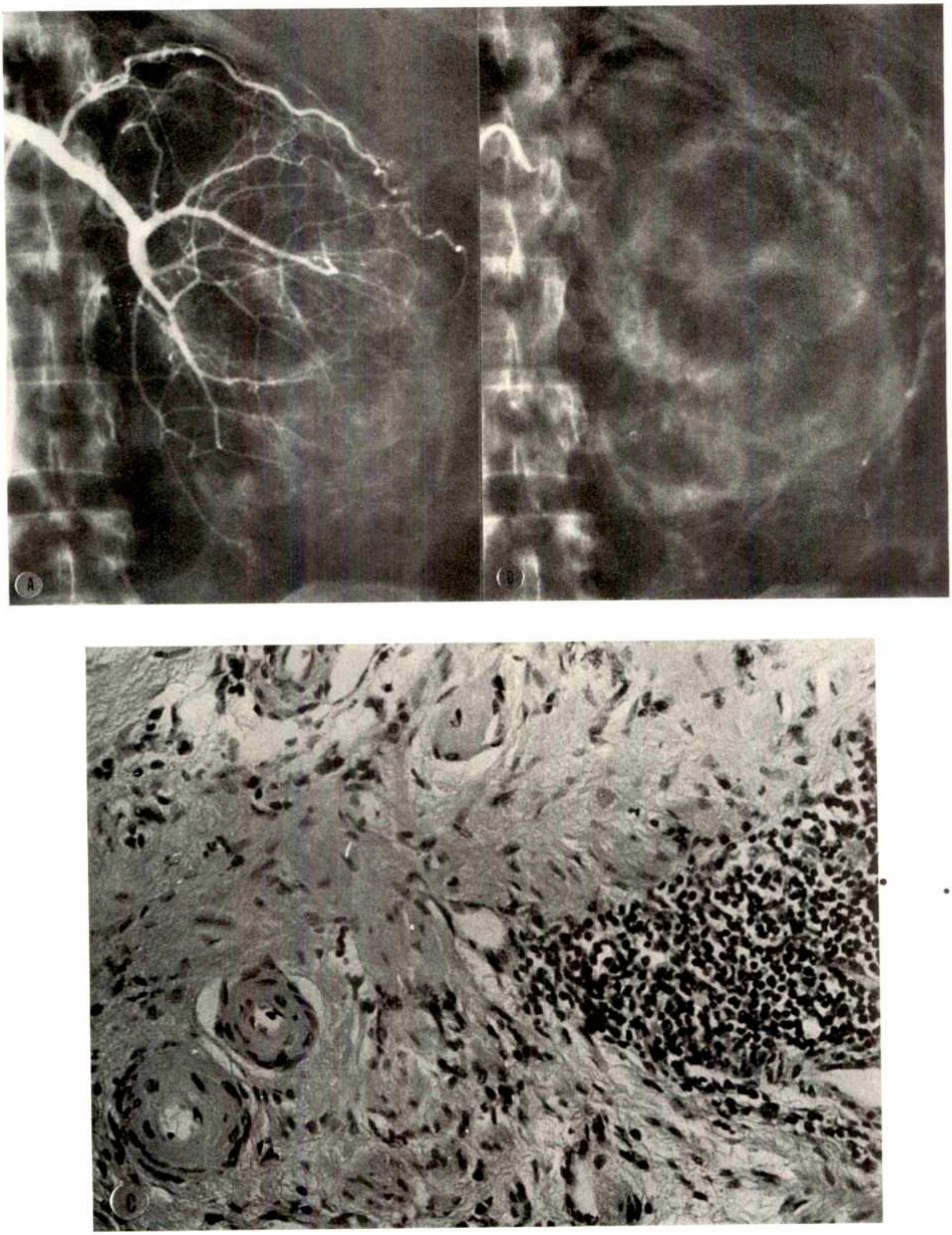


FIG. 8.

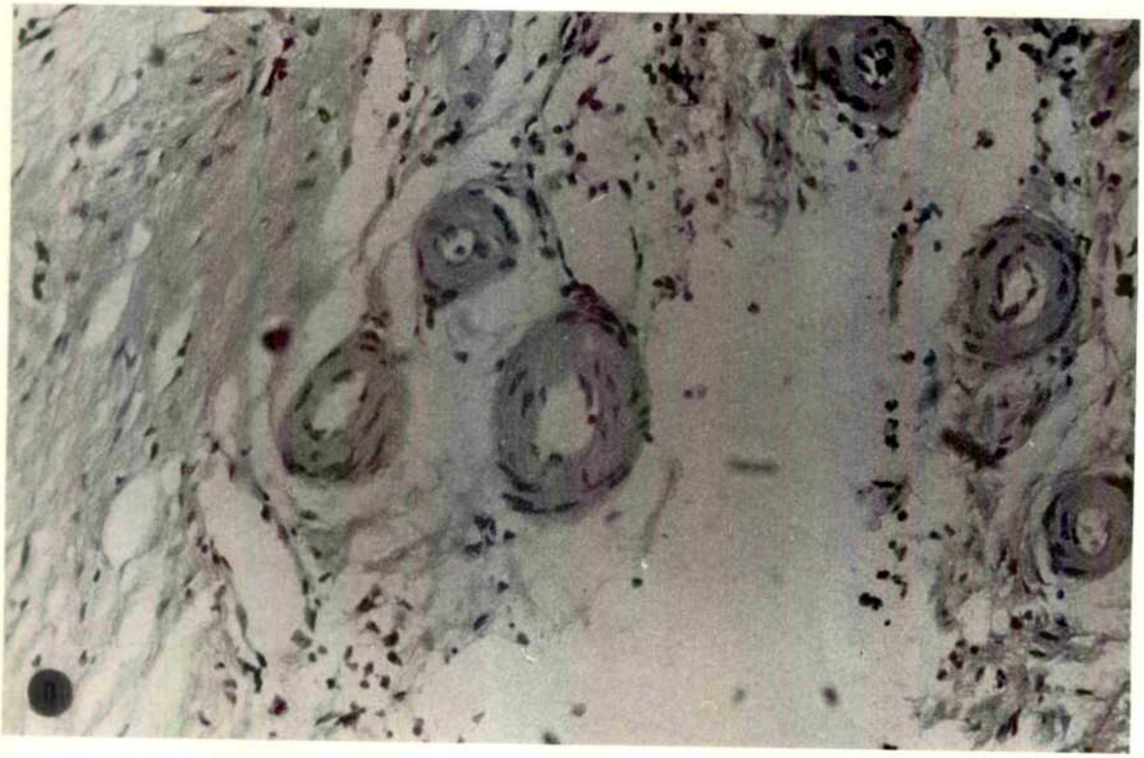


FIG. 8.

Clinically chronic renal infection. Fifty-year-old white female with low back pain attributed to an automobile accident three months earlier. A lumbosacral spine X ray revealed a small left staghorn calculus and small flecks of calcium in the periphery of the left kidney, which was non-functioning on excretory urography. She had sterile pyuria.

(A) Extensive destruction of the renal parenchyma with attenuation of all renal arteries including the main renal artery which measured 6 mm in widest diameter as compared to 9 mm of the right main renal artery. Segmental, interlobar and arcuate arteries are displaced. The renal capsular artery is markedly enlarged and tortuous.

(B) The nephrogram is pale throughout with inflammatory blushes surrounding lucent areas. Prominent capsular veins.

(C) Lymphocytic infiltrate in the renal cortex, intimal and medial thickening and perivascular fibrosis in interlobar arteries. (H & E, 1000 ×)

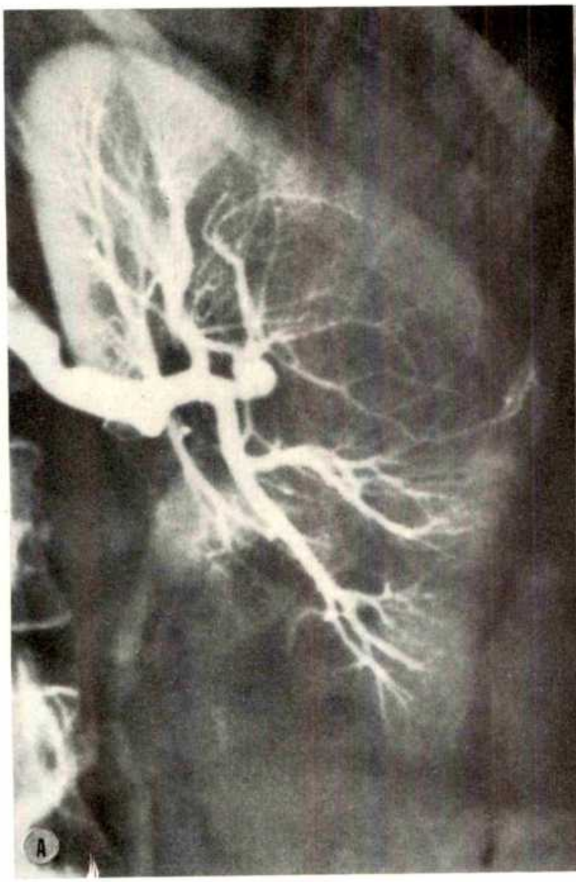
(D) Multiple enlarged capsular branches in Gerota's fascia. At nephrectomy peri-renal inflammation and severe chronic pyelonephritis with extensive parenchymal destruction were found. (H & E, 1000 ×)

parenchymal stain alterations consisting of mottling, streaking and loss of the cortical definition (Figs. 1B, 2B, 4B, 5B, 7B, 8B, 10B, 11B) or complete absence of parenchymal staining (Figs. 3B, 10A). (3) inflammatory staining in the periphery of the infectious process (Figs. 2B, 5B, 6B, 7B, 8B, 9B, 10B, 11D).

Our overall diagnostic accuracy was 64%. In 22 examinations from 1969 to 1973 before the study began a correct preoperative diagnosis was made in 11 cases (50%). In the subsequent 22 cases after 1974, a correct diagnosis was made in 17 cases (77%). In the last two years a correct diagnosis was made in ten out of ten cases. The only two cases missed in the last three years had complete obliteration of the main renal artery due to renal destruction by chronic infection (Fig. 13A). Clinical information was available in each case. During the prospective study series two false positive diagnoses were made: one in a renal capsular sarcoma in which the patient presented with acute flank pain, chills and fever, and a predominantly perirenal mass which had enlarged rapidly during the preceding week as judged by excretory urography. The other, a retroperitoneal lymphoma, encasing but not involving the kidney, was diagnosed as most likely representing a chronic peri-renal abscess.

DISCUSSION

Selective renal angiography has an overall diagnostic accuracy of between 80 and 90% (Young and Morrow, 1972; Lang, 1971). In sharp contrast, in inflammatory lesions preoperative diagnostic accuracy is reported to be 20% or less (Rabinowitz *et al.*, 1972; Doolittle and Taylor, 1963; Goldman *et al.*,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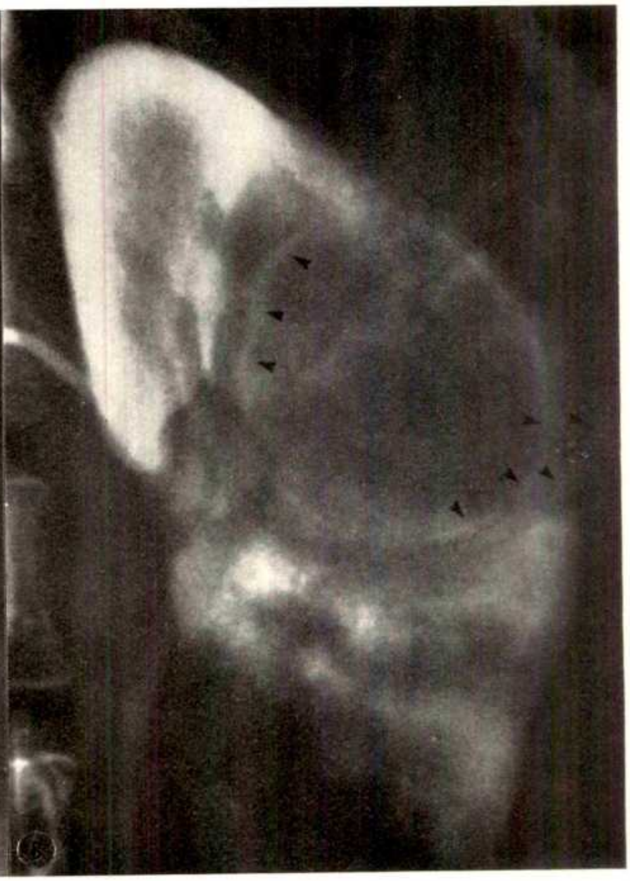
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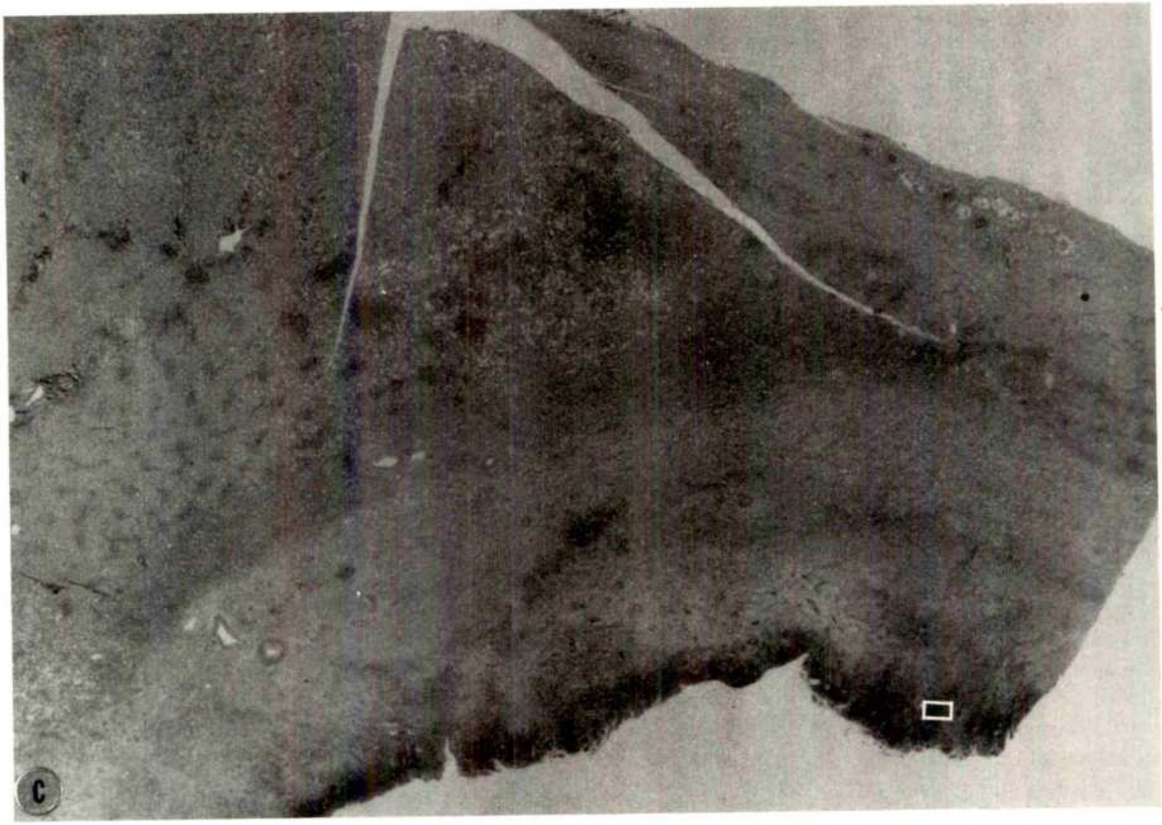
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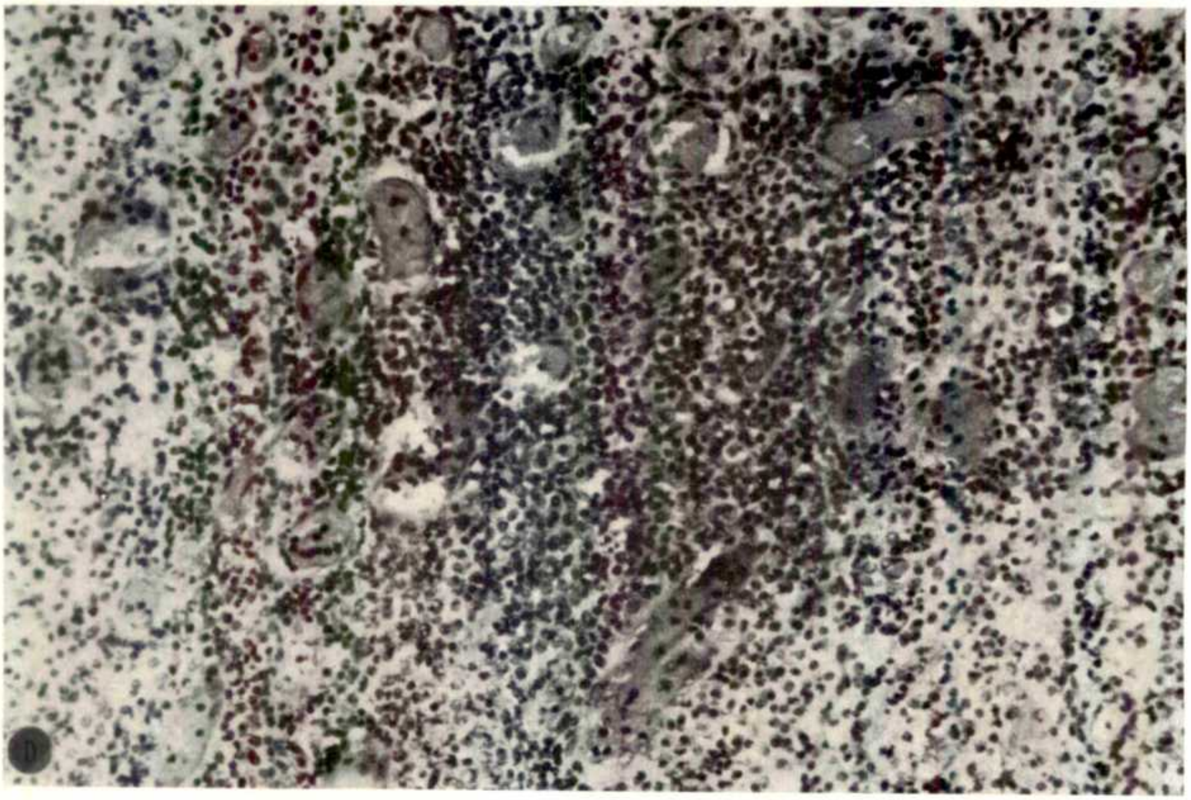

FIG. 9.

Clinically subacute and chronic renal infection. Thirty-five-year-old white female with a six week history of severe left flank pain and fever. Urine from the left kidney grew Proteus mirabilis.

(A) Markedly displaced and attenuated interlobar and arcuate arteries in the upper midsection. (There is an accessory artery to the lower pole.)

(B) The nephrographic blush in this area is faint but there is dense inflammatory staining of the abscess wall (arrows).

(C) The abscess wall adjacent to normal parenchyma. (H & E, approx. 8 ×)

(D) Insert from C shows newly formed arterioles and capillaries responsible for the dense blush in (B). At surgery a large intrarenal abscess was found. (H & E, 1000 ×)

1978). Our experience indicates that much better results can be achieved.

A thorough understanding of the vascular pathophysiologic and anatomic changes in a given disease process greatly enhances the diagnostic skill and confidence of the angiographer. The excellent angiographic and microangiographic histologic correlation in experimental pyelonephritis by Hill and Clark (1972) were a first step in providing the necessary information. These investigators were able to demonsstrate quite convincingly that during the acute stages of inflammation pronounced spasm of segmental and cortical arteries and clogging of postglomerular peritubular capillaries with neutrophils was responsible for slow arterial flow and a delayed and protracted nephrogram. They also observed that in the chronic stages vasoconstriction disappeared and gave way to spiraling or obstruction of arteries subsequent to fibrous scar formation with a resultant pallid and transient nephrogram. Our own histologic observations and correlation with angiographic findings in clinical material substantiate and expand their findings:* In addition to vasospasm and clogging of postglomerular peritubular capillaries, we observed acute vascular necrosis in early inflammation and saw the vasospasm extend to the main renal artery. In subacute and chronic inflammation we observed intimal and medial thickening along with fibrous obliteration of arteries as the correlate of angiographic attenuation of renal vessels. In addition we observed newly formed arterioles and capillaries in the abscess periphery and propose that they are the histologic correlate for the dense inflammatory blush seen angiographically in the late nephrographic phase. This blush is extremely rare in non-inflammatory conditions and should be considered strongly suggestive of an inflammatory process.

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*Although material obtained through nephrectomies may seem to be biased toward more severe and advanced inflammation, we usually found all stages of the inflammatory process in a single specimen.

Further important diagnostic clues can be gained from changes in the renal capsular complex, peri-pelvic, ureteric and retroperitoneal arteries. These vessels react to an inflammatory insult with pronounced vasodilatation in stark contrast to renal parenchymal arteries which reduce in calibre. The result is a striking reversal of the normal situation where renal parenchymal arteries up to the arcuate level are larger than the capsular arterial complex. This reversal, which we found in 16 of 44 examinations, has not been emphasized previously. We like to refer to this phenomenon as renal cortical capsular arterial discordance. In our experience this finding is highly suggestive of but not specific for renal and peri-renal inflammation. We have encountered in our practice one case of primary renal amyloidosis and one case of acute tubular necrosis which gave a similar appearance. McCormick and Cho (1977) have described similar findings in one case of renal amyloidosis. Ambos *et al.* (1977) described a metastatic squamous carcinoma from the lung with a similar angiographic finding.

Sporadic reports in the literature described early draining veins (Salmon and Koehler, 1967; Coombs *et al.*, 1971). We were not able to detect early draining veins in our material and join in this respect the ranks of others (Rabinowitz *et al.*, 1972; Caplan *et al.*, 1967; Koehler, 1974; Giustra *et al.*, 1971; Young and Morrow, 1972; Becker *et al.*, 1967). Since the blood flow through inflammatory lesions is slow as indicated by the contrast persistence in arteries long

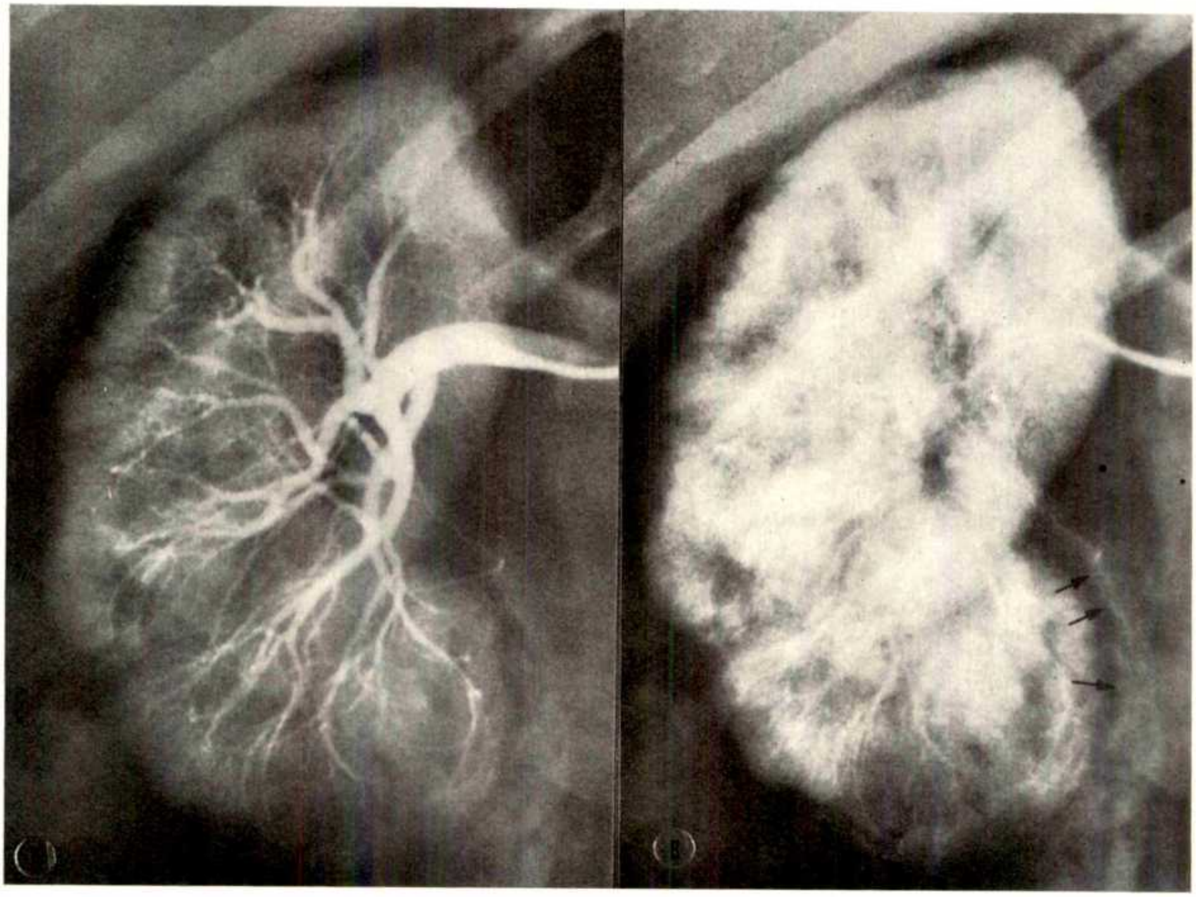


FIG. 10.

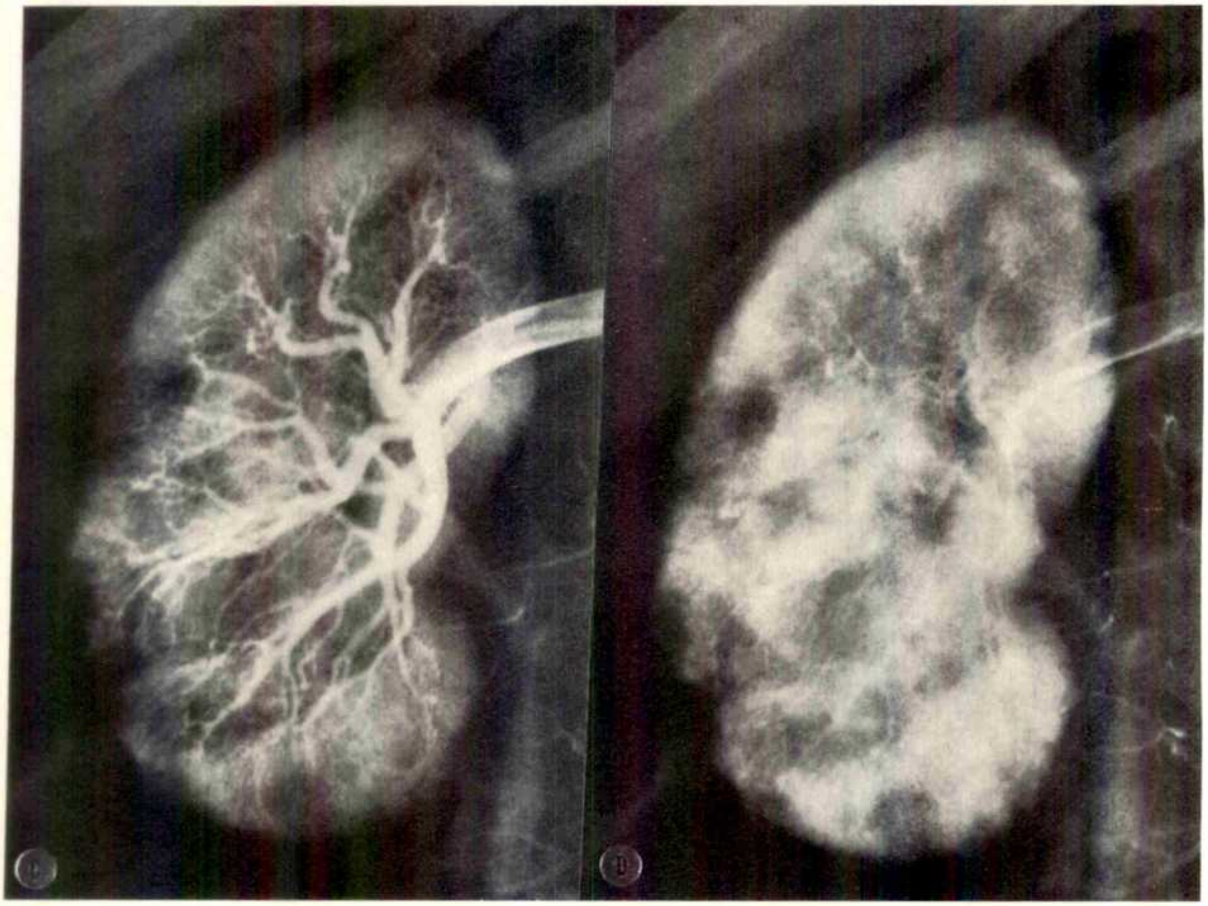


FIG. 10.

Clinically chronic renal infection. Forty-four-year-old black woman with a six month history of bilateral flank pain, recurrent chills and fever. Urine culture from each kidney grew E. coli.

(A) Interlobar and arcuate arteries in the lower pole are displaced and attenuated. Small cortical filling defects are seen in the upper lateral border. The periureteric vessels are enlarged.

(B) Eight seconds after contrast injection there is persistent arterial filling in the lower pole. The cortical definition in the lower pole and the upper lateral border is indistinct. Prominent periureteric arteries and inflammatory blush are seen along the proximal ureter.

(C) Six weeks later after extensive antibiotic therapy the arterial displacement in the lower pole is reduced and the cortical filling defects along the upper lateral border are no longer appreciated.

(D) The cortical definition of the lower pole is more distinct now and the upper lateral cortex is normal. Note the disappearance of the earlier prominent periureteric vessels. The patient required a nephrectomy of the opposite kidney due to advanced inflammatory disease.

FIG. 11.

Clinically chronic renal infection. Thirty-three-year-old black male with frequent episodes of right flank pain over the last five years. A renal arteriogram performed at another institution was interpreted as "tumour in the right upper pole". The patient refused surgery and presents now with back pain, fever and chills. At cystoscopy pus was seen extruding from the right ureteral orifice.

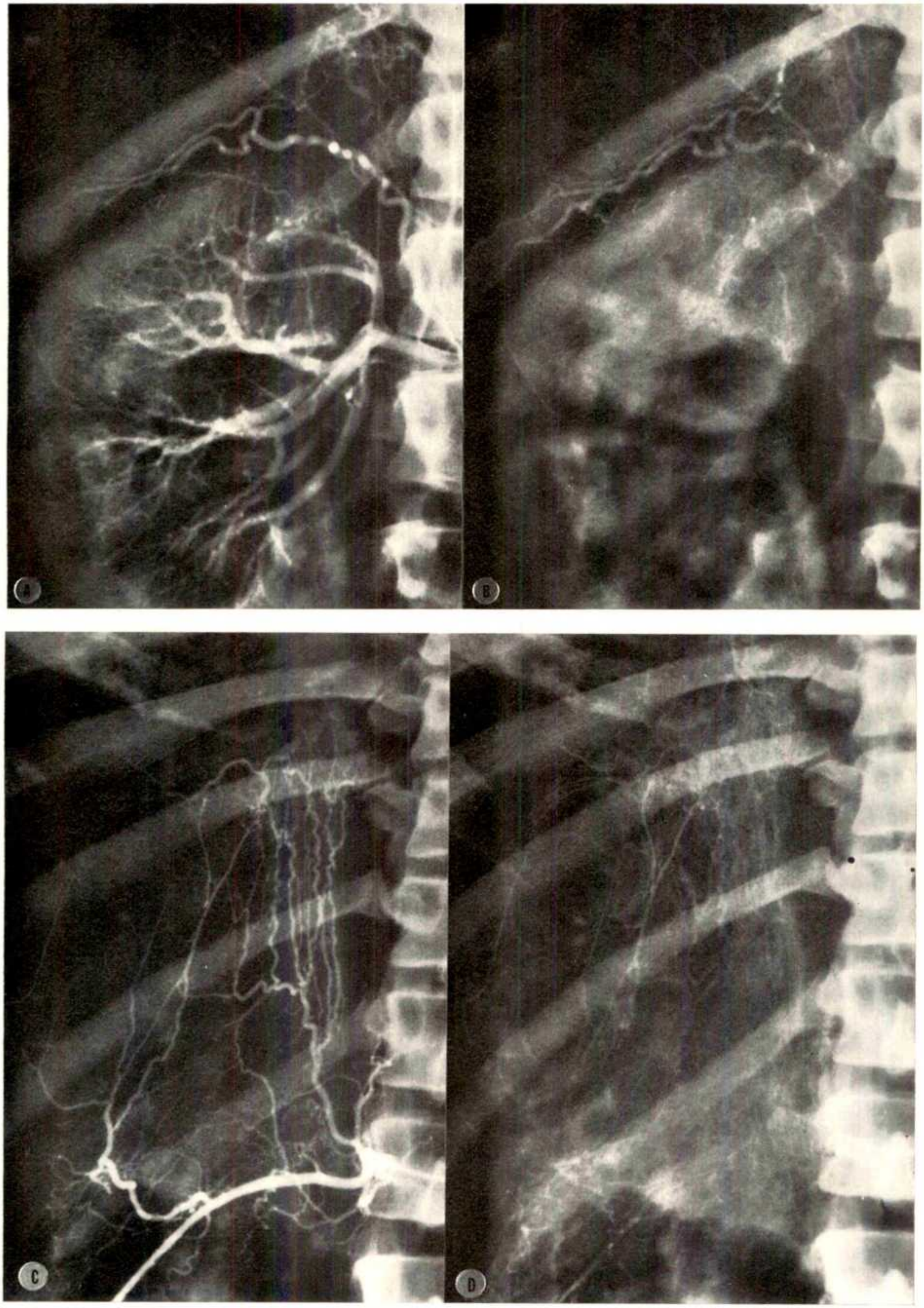
(A) The upper pole capsular artery is markedly enlarged, tortuous and branches frequently. The inferior adrenal artery exhibits similar changes. The underlying arcuate and interlobar arteries are attenuated and displaced. There is lack of cortical opacification.

(B) Slow flow is indicated by arterial contrast persistence at six seconds after injection. There is loss of cortical definition.

(C) Injection of the first lumbar artery reveals extensive inflammatory neovascularity in the retroperitoneum extending from the upper renal pole behind the liver to the dome of the hemidiaphragm. The arteries are tortuous but taper and branch normally.

(D) Eight seconds after contrast injection there is a prominent inflammatory blush. A large firm abscess extending from the upper pole of the right kidney behind the liver to the dome of the right hemidiaphragm was incized and a large collection of purulent material drained.

Selective angiography in renal and peri-renal inflammatory lesions: correlation with histopathology



into the nephrographic phase, we entertain doubts that the inflammatory lesion itself will be drained prematurely.

Although many of the histologic and pathophysiologic vascular changes in inflammation are quite specific for the process, their angiographic correlate does not enjoy the same uniqueness. Thus, vascular attenuation by spasm, fibrosis or intimal hyperplasia cannot be distinguished angiographically from attenuation by a desmoplastic neoplastic process. Similarly, capsular arterial enlargement in response to inflammation cannot be distinguished from enlargement in response to neoplastic blood demand. Occasional cases will continue to constitute a difficult diagnostic problem. Our experience indicates, however, that with close attention to all dynamic and morphologic changes on high quality selective renal angiograms the diagnosis of renal inflammatory lesions can be made with a level of confidence that approaches that achieved in cysts and neoplasm.

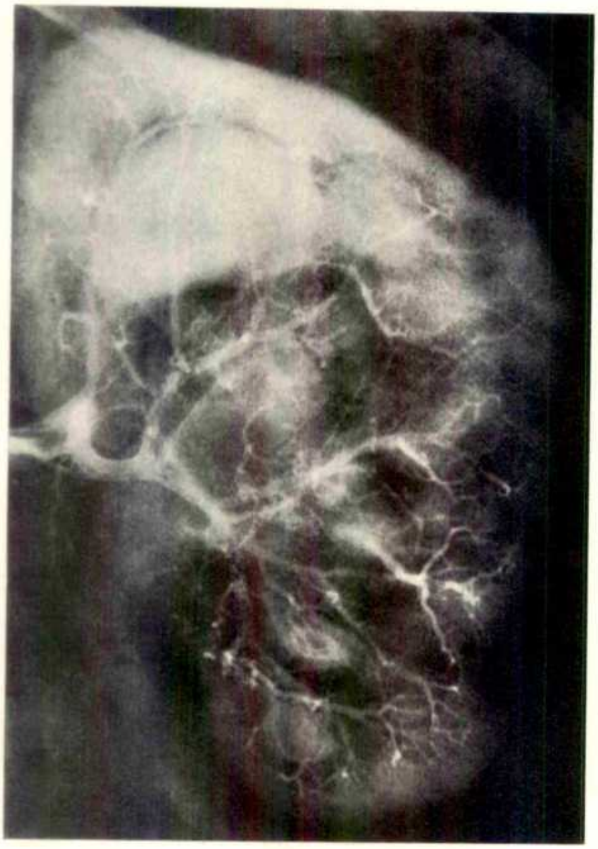


Fig. 12.

Clinically chronic renal infection. Fifty-three year old white male with solitary left kidney with staghorn calculus and long history of repeated renal infection. Recent onset of fever and left flank pain. Urine culture grew Proteus. Peripelvic vessels are tortuous with abrupt changes in course. Renal pelvic biopsy during pyelolithotomy revealed severe acute and chronic inflammation.

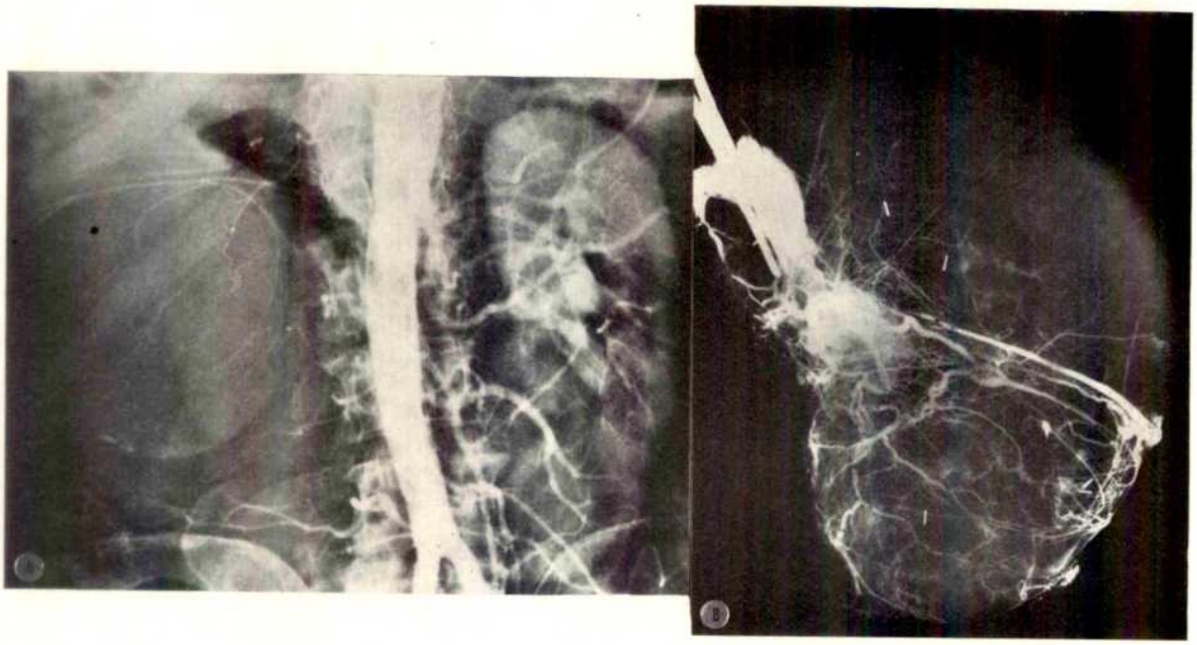


Fig. 13.

Clinically chronic renal infection. Fifty-five-year-old white male with three to four year history of right flank pain. Excretory urography revealed a horseshoe kidney the right side of which was calcified and non-functioning.

(A) There is no right renal artery or renal parenchymal vessels. Instead prominent capsular vessels stretch over a large round avascular mass.

(B) Contrast injection into the artery of the resected specimen reveals a prominent capsular arterial network. At surgery a large cystic structure containing 2100 cc of cloudy brown fluid with areas of inflammation but no identifiable renal tissue was removed.

Acknowledgments

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Book reviews

Clinical Computer Tomography—Head and Trunk. Edited by A. Baert, L. Jeanmart, and A. Wackenheim, pp. x+258, illus. 1978 (Springer-Verlag, Berlin), DM.78.00/$35.90. ISBN 3-540-08458-4.

This soft-cover book is a collection of papers presented at a two-day meeting organized by CEPUR in Luxembourg, March 1977. CEPUR (College d'Enseignement Post-Universitaire de Radiologie) is a medical association concerned with the promotion of advanced courses in radiology. All the papers were contributed by the University Hospitals of Ancona, Leuven, Montpellier, Bruxelles and Strasbourg. The collection does not claim to be a comprehensive review of computed tomography but rather to deal with selected clinical problems.

The volume contains a technical introduction of 16 papers on various aspects of brain scanning (but not trauma) and eight on CT of the trunk. The last group represent the results of early experience and a number suffer from the disadvantage of viewing body sections from above and not below as is the international convention. Despite this criticism, the collection of papers represents a valuable record of the radiological course and a useful addition to the CT literature. Some good basic principles are incorporated within the various papers and the illustrative content is enhanced by the high standard of Springer Verlag publishing.

The editors and authors deserve credit for their industry but inevitably the increasing number of scientific journals concerned with CT have covered similar ground and witnessed further advances over the succeeding two years.

Ian Isherwood.

Super-selective arteriography of the external carotid artery. By R. Djindjian and J-J. Merland, pp. xvii+550, illus., 1978 (Springer Verlag, Berlin, Heidelberg, New York.) DM430/$215.
ISBN 3-540-08118-6.

Neuroradiologist and angiographers will be familiar with the publications of these authors. The present work is up to their usual standard of excellence. It is indeed sad that Professor Rene Djindian died before its success could be acclaimed.

The book deals in detail with the technique of super-selective angiography of the external carotid branches, with the normal anatomy as shown by the precise definition possible with super-selective angiography, with the pathological processes revealed by the method in the head and neck and finally with therapeutic embolization.

Although it is a reference book, mainly based on the work of the authors and their collaborators, and an extensive review of the literature, the text, which is beautifully illustrated by subtraction angiograms and accompanied by explanatory line drawings makes easy and compelling reading. It will be of interest not only to angiographers, neuroradiologists and others involved with the neurosciences, but also to facio-maxillary, ENT and plastic surgeons and opthalmologists.

The book is a land-mark in the study of the external carotid artery; it sets out clearly what has been achieved so far, providing the basis of pointing the way for further research.

B. Kendall.

1979, *British Journal of Radiology*, 52, 558–561

Bronchial artery embolization in the control of massive haemoptysis

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Abstract

Bronchial artery embolization is a useful palliative treatment for life-threatening haemoptyses where surgery is contra-indicated. Patients presenting with haemoptyses complicating cystic fibrosis and aspergilloma have been embolized. Control of haemoptysis was achieved in the former, but late recurrence of haemoptysis in the latter led to asphyxiation.

In massive haemoptysis surgery may be contra-indicated when there is severe bilateral pulmonary disease, in the presence of a non-resectable carcinoma, or when recurrent bleeding follows surgery. The vascular supply in most instances originates from the bronchial circulation, and it has been established that the bronchial arteries may be safely interrupted without danger of significant bronchial or pulmonary ischaemia (Stone *et al.*, 1966). Extensive use of therapeutic bronchial embolization has been reported by Remy *et al.* (1977), and smaller numbers have been reported by Wholey *et al.* (1976), Bookstein *et al.* (1977), Schuster and Fellows (1977), and Bredin *et al.* (1977). We wish to report two further patients with severe repeated haemoptyses complicating bilateral pulmonary disease, who were treated by embolization.

Case Reports

Case 1

A 40-year-old female patient had a 19 year history of progressive pulmonary sarcoidosis, with secondary fibro-bullous disease. She had developed a large right upper lobe cavity, which contained an aspergilloma (Figs. 1 and 2), and she was in chronic respiratory failure. On this occasion she

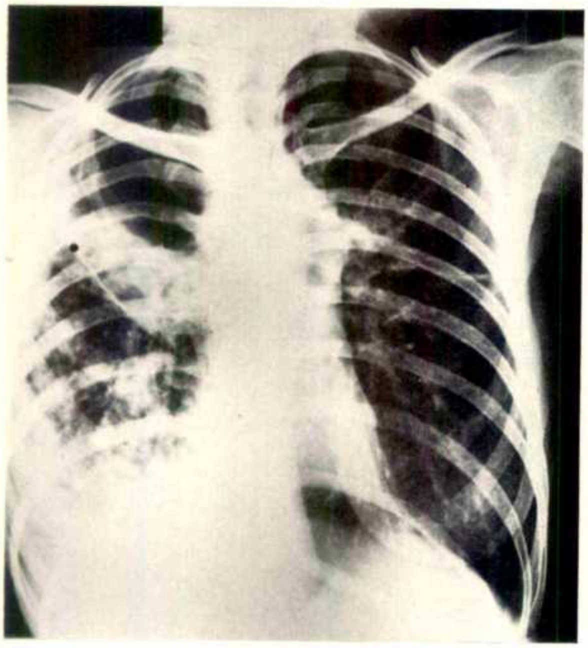

Fig. 1.

Extensive bilateral fibro-bullous disease. Right apical bulla and basal consolidation.

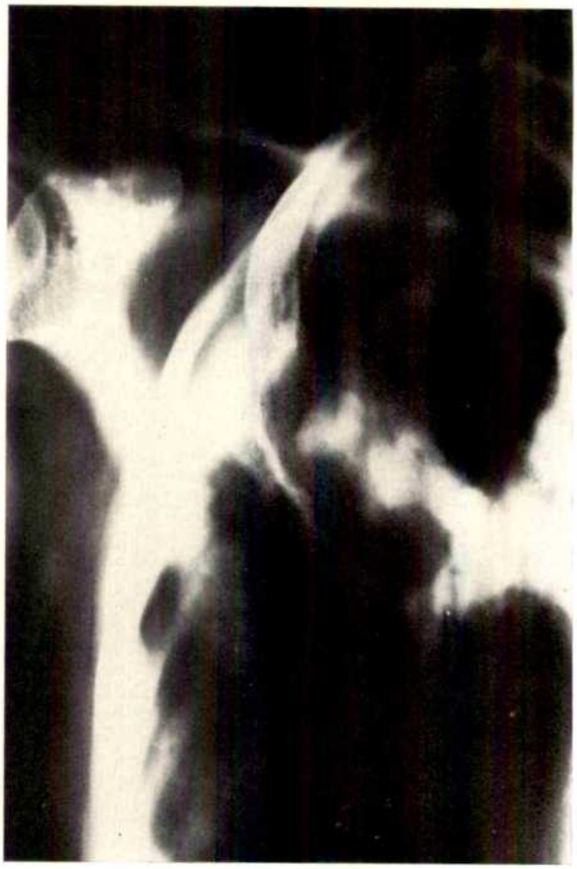

Fig. 2.

Tomogram of right upper lung field; large cavity containing aspergilloma.

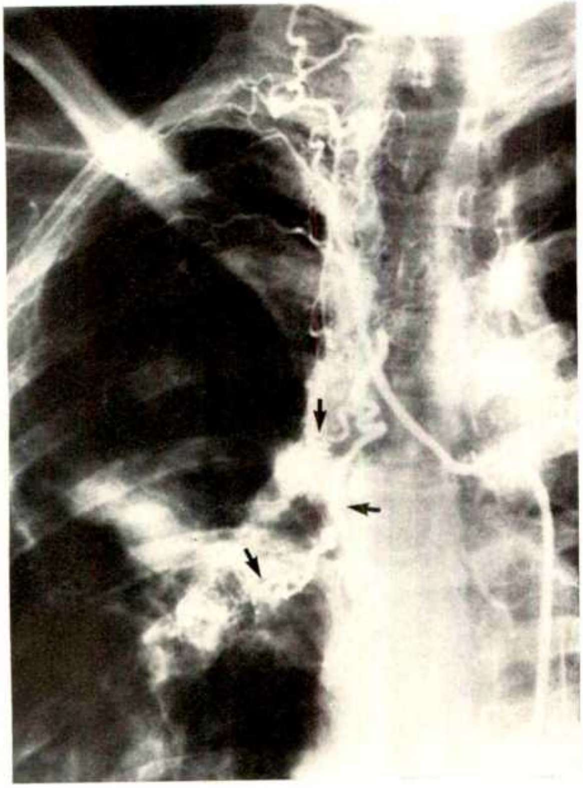

FIG. 3.

Selective right bronchial angiogram. Enlarged tortuous arteries extending to aspergilloma (arrows).

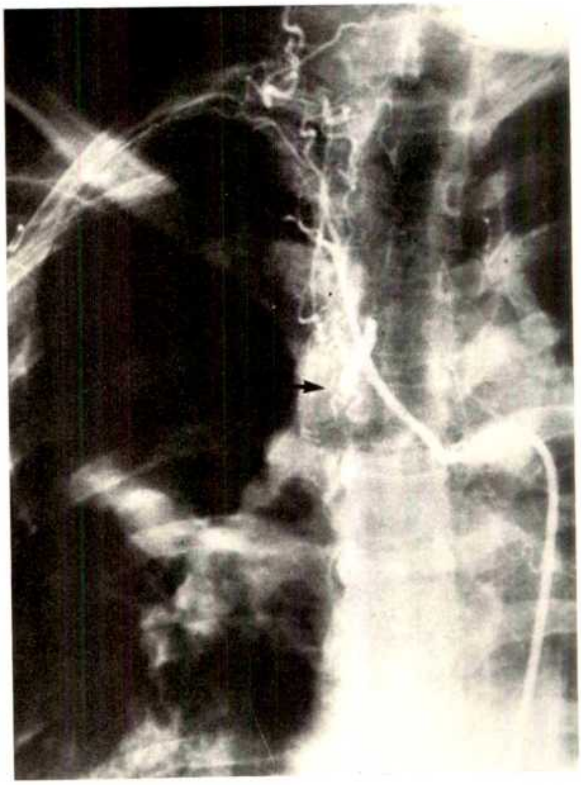

FIG. 4.

Right bronchial angiogram post embolization. Main vessels are occluded (arrow).

was admitted following daily severe repeated haemoptyses. The source of blood loss was found on bronchoscopy to be in the right upper lobe. Her clinical state deteriorated rapidly, she was extremely dyspnoeic at rest, and haemoptyses persisted. Surgical intervention was not considered possible. Selective catheterization of the right bronchial artery was performed, using a French −7 endhole catheter. A common trunk to the right second and third inter-costal arteries and bronchial artery was found. There was no contribution to the anterior spinal artery. The bronchial artery was hypertrophied and tortuous, and a minor vascular blush was seen in the region of the aspergilloma. Extravasation of contrast was not demonstrated (Fig. 3). Embolization of the bronchial artery was performed, using oxycel (oxydised cellulose) fragments, as previously described (Mac Erlean *et al.*, 1978) (Fig. 4). The patient did not experience any discomfort, and there were no complications. Immediate cessation of haemoptysis occurred, and there was no recurrence during the following six days. On the seventh day, haemoptysis recurred, which rapidly led to asphyxiation and death.

Case 2

A 17-year-old male, with proved cystic fibrosis was admitted shocked and hypotensive, following large haemoptyses over the previous 36 hours (Fig. 5). Over the next five days he had several further haemoptyses, amounting to a total of three litres, and was treated with whole blood transfusions. Bronchoscopy indicated that the bleeding originated on the right side. He continued to have large haemoptyses, and was intermittently shocked, hypotensive and hypoxic. It was decided to perform bronchial artery embolization, using the same technique as above (Figs. 6 and 7).

Although the patient was persistently hypotensive immediately before and during the procedure, embolization was tolerated well. His haemoptyses ceased immediately, but following the procedure, he developed severe respiratory failure, his pO_2 falling to 3.7 kPa and pCO_2 to 10.3 kPa. He was managed over the next 24 hours with 28% oxygen by face-mask and nikethamide infusion. Post-operatively, it was noticed that the patient had developed a raised erythematous, and later, necrotic area of skin between the ninth and tenth ribs on the right side. This was interpreted as an area of skin infarction, secondary to occlusion of an intercostal artery by embolic material.

Twenty-four hours after embolization, he also developed weakness in the right leg, and retention of urine. On detailed neurological examination he had a slight right facial weakness, and reduced power in the right arm. Subsequent neurological examination has shown a persistence of weakness in the right leg, right arm and face, and an extensor plantar response on the right side. Neurological opinion was that this represented cerebral infarction, due to shock and hypoxia. It was considered not to be due to embolic material, because of the site of the embolization, and the temporal relationship of the cerebral lesion.

Haemoptysis ceased completely for ten days, but then recommenced in small amounts—50–100 ml daily. He was started on Prednisone, 40 mg, alt. die. Over the next week, the haemoptysis ceased, and has not recurred, up to three

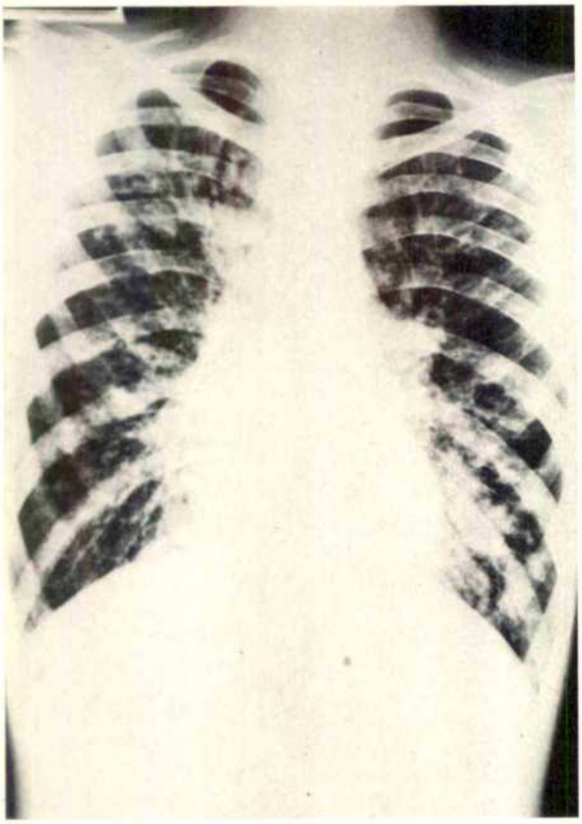

FIG. 5.

Extensive bilateral interstitial changes, consistent with cystic fibrosis.

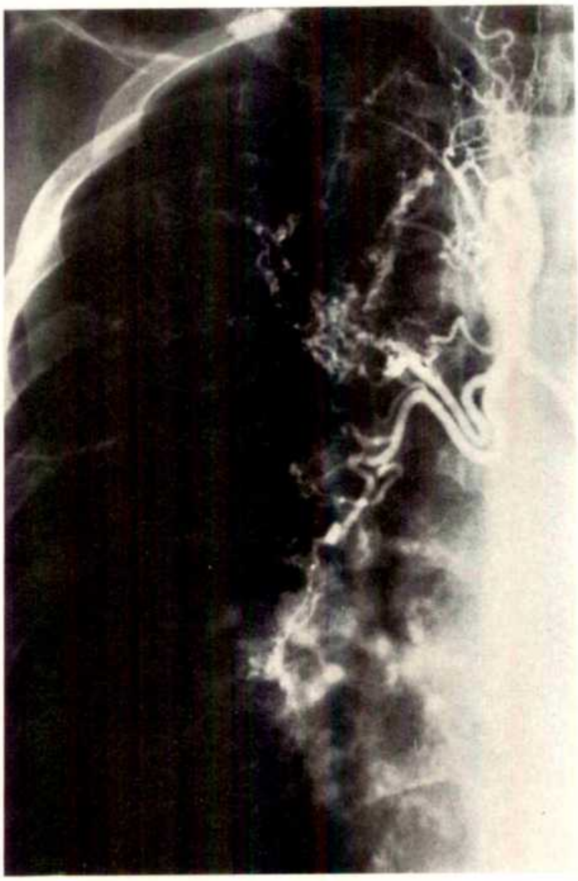

FIG. 6.

Selective right bronchial angiogram. Grossly enlarged and tortuous bronchial arteries.

months later. He is left with slight residual weakness in the right leg. The embolic skin lesion on his back has completely resolved.

DISCUSSION

Of 49 patients with active haemoptyses treated by Remy *et al.* (1977), bleeding stopped in 41, but recurred in six patients between two and seven months post-embolization. Wholey *et al.* (1976) reported control of active haemoptyses in four patients, but long-term follow-up and incidence of complications were not reported. Bookstein *et al.* (1977) treated a single patient successfully, but repeat haemoptyses occurred at five weeks and five months, necessitating repeat embolization. Schuster and Fellows (1977) used embolization in seven patients with intractable haemoptyses complicating cystic fibrosis. Two of these seven patients had recurrent massive haemoptyses within ten days, requiring in each case three further embolization procedures before haemoptysis ceased. Bredin *et al.* (1977) reported successful embolization in a patient with bronchiectasis. Temporary cessation of bleeding was followed by massive haemoptysis, which was then immediately controlled by interruption of the ipsilateral pulmonary artery by a Swan-Ganz balloon catheter. Deflation of the balloon catheter was immediately followed by recurrence of haemoptysis, and reflation once again promptly interrupted blood loss.

Temporary cessation of life-threatening haemoptyses was achieved in these two patients. Recurrence of bleeding seven days after embolization in our first patient, with an intra-cavitary aspergilloma, led to asphyxiation and death. Remy *et al.* (1977) found that recurrence of bleeding was more common in patients with aspergilloma, and suggested that this was probably due to systemic collateral supply from the subclavian and axillary arteries. The case of Bredin *et al.* (1977) amply demonstrated the importance of broncho-pulmonary artery anastamoses in patients with chronic cavitary disease, and it is

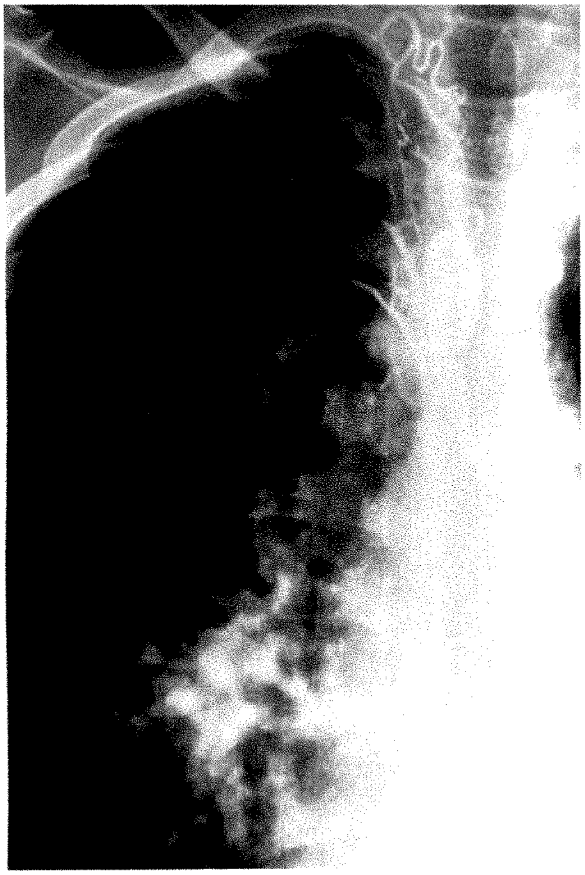

Fig. 7.

Right bronchial angiogram post embolization. Main bronchial vessels have been occluded.

clear that in some instances, successful obliteration of the bronchial circulation may produce disappointing results, due to subsequent bleeding from the pulmonary circulation. Haemoptysis as a complication of cystic fibrosis is now found more frequently, with the increased life-expectancy of these patients. In the single case reported here, control of haemoptysis allowed successful management, with no recurrence of bleeding over three months.

Peripheral embolization is a potential hazard of bronchial artery embolization, and can be guarded against only by meticulous technique and constant monitoring following introduction of embolic particles. Of possible greater significance is local cord damage, as in 5% of patients a common origin to the anterior spinal artery is present (Kardjiev *et al.*, 1974). The artery of Adamkiewicz, supplying the anterior spinal artery, must be carefully sought on the selective bronchial angiogram, as its presence is an absolute contra-indication to embolization. Remy *et al.* (1977) reported a minor degree of bronchial necrosis in a single case, and retrosternal pain in a minority of cases. They attributed these phenomena to embolization of small bronchiolar branches, and oesophageal branches of the bronchial artery respectively. The area of skin necrosis found in our second patient has not previously been described. It represents an unusual infarction in view of the extensive collateral circulation between the intercostal vessels.

Trans-catheter embolization in haemoptysis is palliative, and revascularization may occur following reabsorption of the materials currently used. The possible future role of this technique in haemoptysis will depend upon careful patient selection and upon improved materials for embolization. It is of use in patients presenting with severe haemoptyses who have temporary or permanent contra-indications to surgical intervention. It may be of benefit in enabling patients who are not fit for surgery to undergo conservative management, with possible definitive surgery being performed at a later date.

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Pancreatic ultrasound—a systematic approach to scanning technique

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ABSTRACT

The pancreas remains one of the more difficult organs to visualize but ultrasound can be successful in nearly 90% of patients. A systematic technique for identifying and delineating the pancreas is described and has been verified on over 500 patients to date. The success of the technique depends on an accurate knowledge of the vascular relations of the pancreas and on correct adjustment of the ultrasound equipment. This paper is intended to help ultrasound practitioners achieve both these ends.

With the steady increase in the incidence of pancreatic carcinoma in western countries (Registrar General 1966; 1972) (Krain, 1972), and the continued prevalence and improved awareness of inflammatory pancreatic disease, increased efforts are being made to perfect pancreatic imaging systems. In recent years the potential role of ultrasound has been investigated by many workers, but without the use of grey scale display it was considered almost impossible to visualize the normal pancreas (Filly & Freimanis, 1970; Burger & Blauenstin, 1974; Stuber *et al.*, 1972). The advent of grey scale display has greatly improved visualization of the normal pancreas, being successful in 89% of 328 patients (Haber *et al.*, 1976) and in 82% of 135 patients (Weill *et al.*, 1977). The different success rates quoted by various authors may well reflect the adequacy of the differing scanning approaches used, all authors agreeing that the presence of upper abdominal bowel gas is currently the major cause of failure.

The variable anatomy of the pancreas (Kreel *et al.*, 1973; Barton, 1976) is a further source of difficulty, but the relatively constant vascular relations of the pancreatic body have been emphasized by Leopold, (1975) and Sample, (1977) who also pointed out their value in locating the pancreas.

This paper describes a development of Leopold's method which we have found valuable in outlining the pancreas, and the technique will be described systematically so that anyone practising clinical ultrasound may use the technique themselves.

It must be emphasized that because of the complex and variable shape of the pancreas it is seldom possible to outline the entire length of the organ on a single scan, or to demonstrate more than 60–70% of its volume in most patients.

MATERIALS AND METHODS

All scans were performed with a conventional Nuclear Enterprises Diasonograph (NE 4102) with grey scale display (NE 4104), or an NE 4200 Diasonograph. A 3·5 MHz focussed transducer is normally employed and all patients are examined in the supine position during normal respiration. The first goal is to establish the level at which the pancreatic body lies, and therefore each examination is preceded by a longitudinal "scout scan" over the aorta and the equipment control settings are adjusted to give mid grey echoes in the liver. No "swept gain delay" is necessary and the "suppression" control (if fitted) should never be used for grey scale work. Later machines include a "dynamic range" control and this should be set to maximum. Longitudinal scans are then performed over the aorta at 2 mm intervals (wider spacing will cause vessels to be overlooked) until one of the major upper abdominal vessels is identified. The level of the pancreas can then be inferred in one of several ways. Scans to the left of the midline may show the coeliac axis or superior mesenteric artery (SMA) (Fig. 1). The body of the pancreas lies about 2–3 cms caudally to the origin of the coeliac axis and

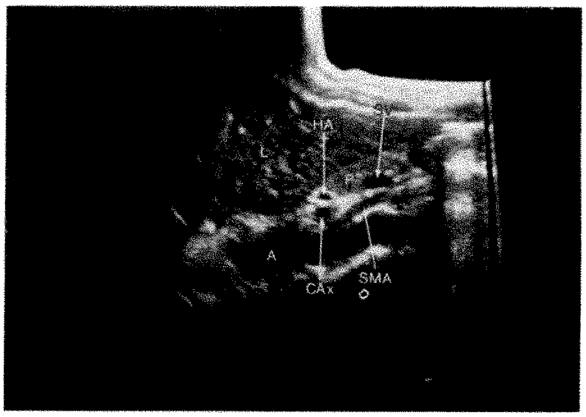

FIG. 1.

Longitudinal scan in midline showing vascular relations of the pancreatic body. A aorta; CAx coeliac axis; HA hepatic artery; L liver; P pancreas; SMA superior mesenteric artery; SV splenic vein.

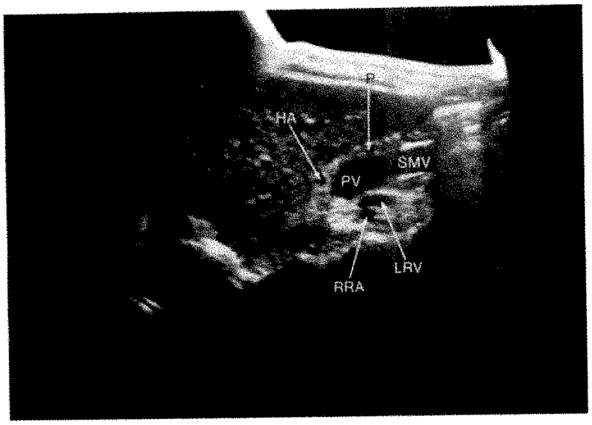

Fig. 2.

Longitudinal scan to right of midline. HA hepatic artery; LRV left renal vein; P pancreas; PV portal vein; RRA right renal artery; SMV superior mesenteric vein.

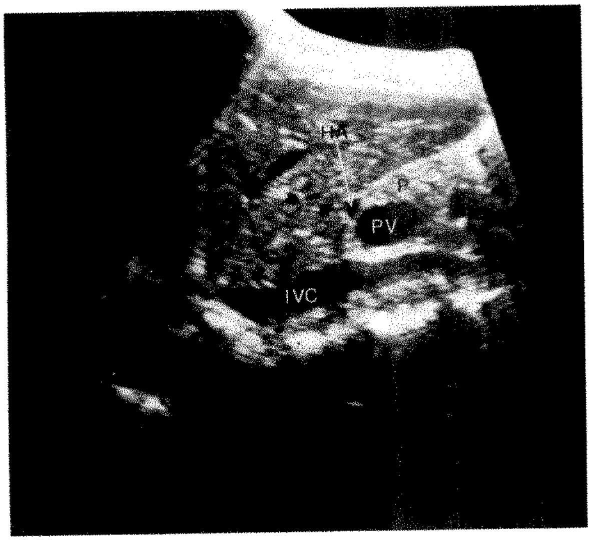

Fig. 3.

Longitudinal scan further to the right of midline showing part of the pancreatic head. HA hepatic artery; IVC inferior vena cava; P pancreas; PV portal vein.

about 1 cm caudally and anteriorly to the origin of the SMA, thus either vessel may be used as a reference. Scans to the right of the midline will show the superior mesenteric vein (SMV) ascending to join the splenic vein and forming the portal vein (Fig. 2). The body of the pancreas lies immediately caudally and anteriorly to this junction. Care must be taken not to apply too much downward pressure on the transducer or the lumen of the SMV may be obliterated. Although the level of the body can be determined accurately by this method the pancreas itself will sometimes not be clearly identified on longitudinal scans. However, when displayed, it can be recognized by the presence of the splenic vein running along either its superior or posterior borders (Fig. 1). The hepatic artery lies along the superior border of the head and body and can be seen on scans in the midline and to the right (Figs. 1, 2 and 3).

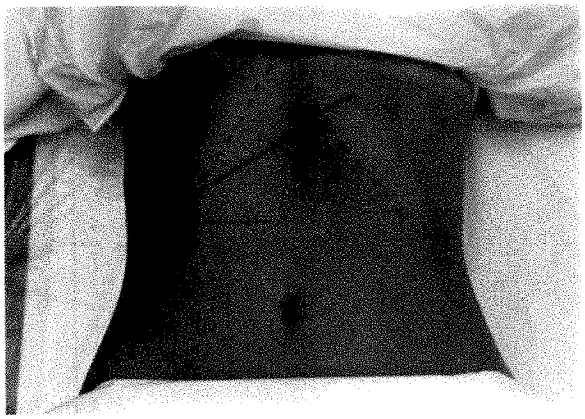

Fig. 4.

Surface markings of a normal pancreas.

The diameters of the above mentioned vessels are all close to the limits of resolution of the apparatus, and thus it is essential to optimize resolution by choosing the correct output and receiver settings. These will vary from one machine to another and from patient to patient and therefore cannot be meaningfully quoted here. In practice we have found that visualization of a 3 or 4 mm vessel may be impaired if the sensitivity is 4 db too high. When scanning during normal respiration a "single pass" technique must be used.

Once the level of the pancreatic body has been determined, transverse scans are performed at this level and vascular landmarks are again sought. It must be remembered that the long axis of the pancreas may vary from a directly transverse position to an angle of up to 45° (θ in Fig. 4), the tail being cranial to the pancreatic head. The initial transverse scan should therefore be performed at an angle of about 20°, and in practice this will permit inclusion of the head and most of the body on one scan in the majority of patients. Several authors (Doust and Pearce, 1976 and Leopold, 1975) have recommended that the scanning frame may be angled cranially to facilitate access to the high pancreas, but we have never found this necessary and often note that this technique would bring the transducer down over bowel gas and lead to a failed examination.

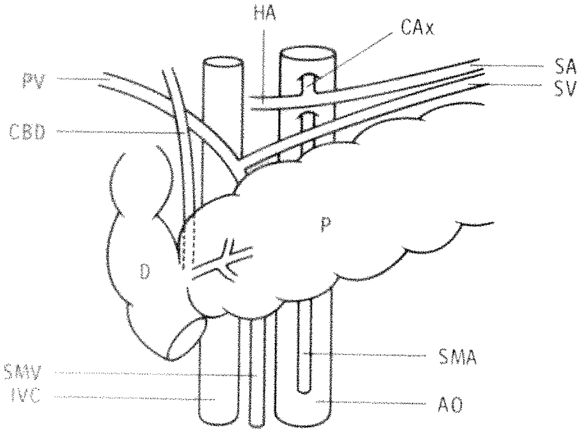

FIG. 5.

Line diagram to show anatomical relations of the pancreas. ao Aorta; CAx coeliac axis; CBD common bile duct; HA hepatic artery; IVC inferior vena cava; PV portal vein; SA splenic artery; SMA superior mesenteric artery; SMV superior mesenteric vein; SV splenic vein.

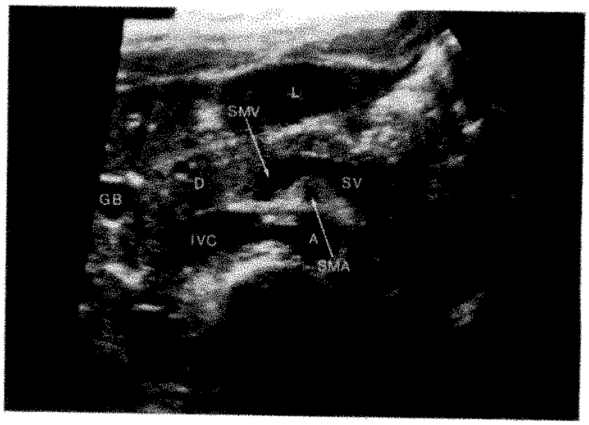

FIG. 7.

Transverse scan at the level of the splenic vein. A aorta; D duodenum; GB gall-bladder; IVC inferior vena cava; L liver; SMA superior mesenteric artery; SMV superior mesenteric vein; SV splenic vein.

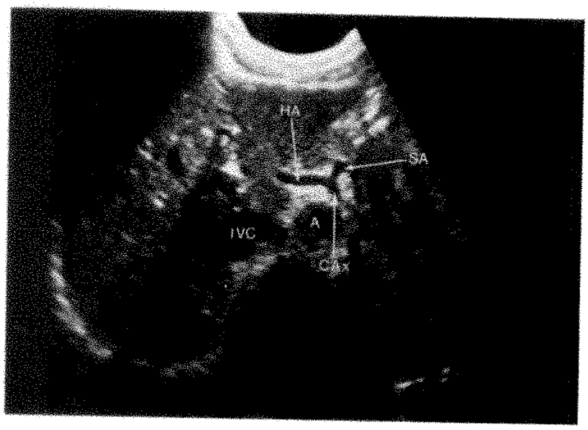

FIG. 6.

Transverse scan at the level of the coeliac axis. A aorta; CAx coeliac axis; HA hepatic artery; IVC inferior vena cava; SA splenic artery.

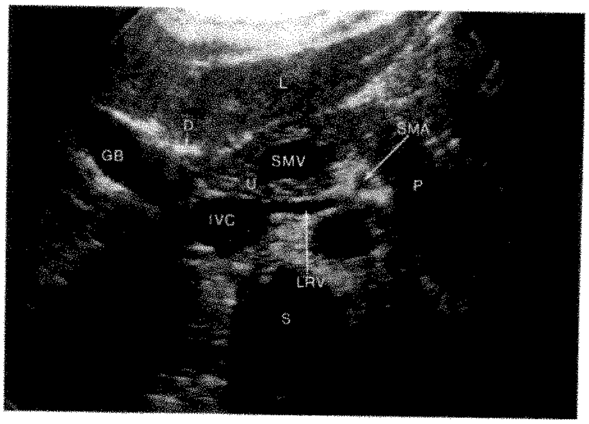

FIG. 8.

Transverse scan of a pancreatic head showing a well formed uncinate process. D duodenum; GB gall-bladder; IVC inferior vena cava; L liver; LRV left renal vein; P pancreas; S spine; SMA superior mesenteric artery; SMV superior mesenteric vein; U uncinate process.

The vessels identified on the longitudinal scan can all be detected on transverse scans and enable the operator to determine the exact level of the pancreas. Figure 5 shows the relative anatomy of the major arteries and veins.

Transverse scans must again be performed at very close intervals, about 2 mm, and it has been found most useful to start at a level judged to be about 1 cm above the upper margin of the body. If the scan is too high the coeliac axis or portal vein may be seen (Fig. 6) whilst more caudal scans will next identify the splenic vein (Fig. 7). The relationship of the splenic vein to the pancreas is variable, it may lie along the upper border, in a groove in the upper border or be posterior to, or even within the pancreas. Once its level has been identified a scan 5 mm caudally will invariably pass through the body of the pancreas, and since the longitudinal dimension of the pancreatic body is about 3 cm, portions of it will be seen on many adjacent scans in this region. The junction of the splenic and superior mesenteric veins (Fig. 7) can almost always be identified and at this level, or just caudally to it, the SMA will be seen in cross section (Figs. 7, 8 and 9). This vessel has a clearly defined wall and is usually surrounded by a small layer of fat as it passes posteriorly to the pancreatic body. These features make it the single most useful landmark in searching for the pancreas on transverse scans, as it can virtually always be identified.

The pancreatic head can readily be identified once the body has been located and its boundaries are usually clearly defined, the anterior and lateral ones being formed by the liver and duodenum, the IVC being the posterior boundary (Figs. 7, 8 and 9). The uncinate process is rather variable but will be seen more frequently as experience in identifying the SMV is gained (Fig. 8) but it seems likely from our experience that in many patients this process is not well formed. Occasionally the normal common bile duct will be seen just anteriorly to the IVC (Fig. 9). Again a single pass technique is normally used, but in patients who are able to hold their breath adequately minimal compounding may be found to improve the image (Figs. 7 and 9).

Occasionally, the presence of gas in the duodenal loop will prevent adequate visualization of the pancreatic head, but a repeat scan just a few minutes later will often be successful.

The tail remains the most difficult portion of the pancreas to outline, primarily as a result of the almost invariable presence of bowel gas lying anterior to it, and secondly due to its very variable length and orientation (Barton, 1976). However, the left renal vein is a frequent posterior relation to the tail and this vessel can often be detected on transverse scans (Fig. 10). It can be identified as an echo free tubular structure coursing anteriorly and medially from the left renal hilum to pass between the aorta and SMA (Figs. 8 and 10). The medial portion of the pancreatic tail lies anterior and lateral to this vessel and is almost invariably greater in AP diameter than the mid portion of the body. In those patients in whom the tail cannot be visualized via the anterior approach, a posterior scan should be attempted (Haber *et al.*, 1976). However, in practice, we have found that the interposed posterior abdominal wall muscles cause considerable beam distortion with consequent loss of resolution, and this limits the use of this approach to that of merely estimating the size of the tail (Fig. 11).

RESULTS

The level of the body of the pancreas, with respect to the vascular landmarks, has proved to be remarkably constant, though it is very difficult to

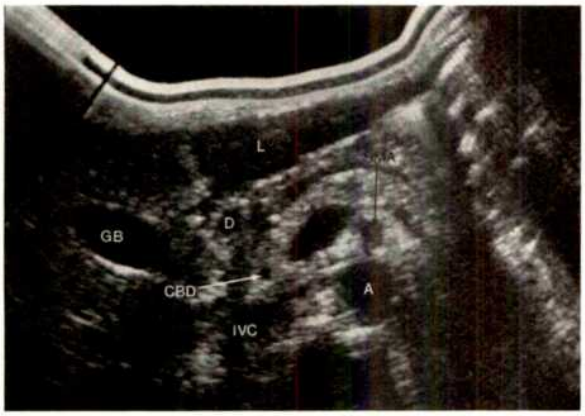

FIG. 9.

Transverse scan of a pancreatic head showing a normal common bile duct. A aorta; CBD common bile duct; D duodenum; GB gall-bladder; IVC inferior vena cava; L liver; SMA superior mesenteric artery.

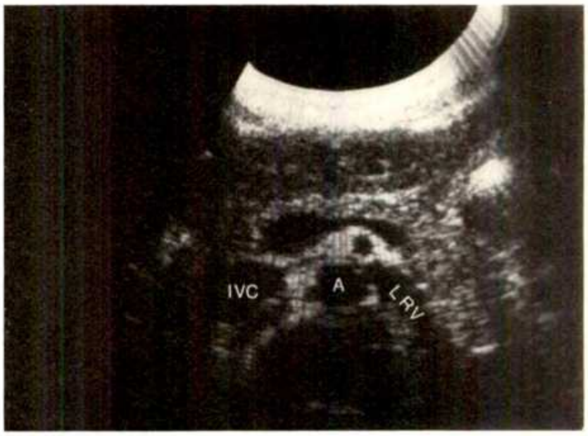

FIG. 10.

Transverse scan of the tail of pancreas showing the left renal vein. A aorta; IVC inferior vena cava; LRV left renal vein; P pancreas.

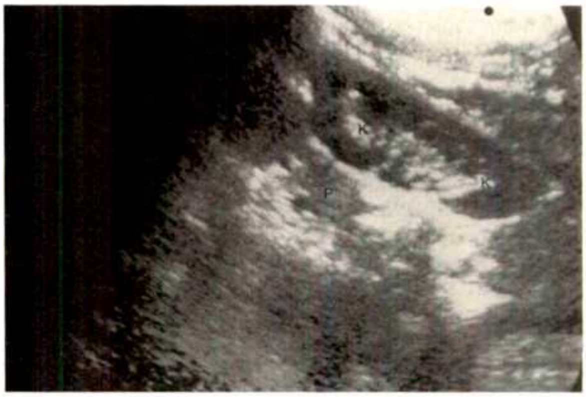

FIG. 11.

Posterior longitudinal scan to show tail of pancreas. K kidney; P pancreas.

relate it to the vertebral bodies accurately, as is the custom in conventional radiology. The variable shape and orientation of the pancreas, and the difficulty in outlining the tail have prevented us from identifying more than about 70% of the pancreatic volume in most patients.

The appearance of the normal pancreas is somewhat variable but in general is fairly homogenous with the average echo amplitude being slightly higher than in the adjacent liver (Fig. 7). However, the relative echo amplitudes will vary with different swept gain settings, different transducer frequencies and in diffuse liver disease.

An analysis of the causes for failure to visualize the pancreas confirms that the presence of gas in the bowel lying anterior to the pancreas was the commonest. This was more often a problem in large or obese patients, but in this group several failures were also noted which were not attributable to gas. Scans on thin patients were almost always successful.

DISCUSSION

The presence of upper abdominal bowel gas remains the single most important factor preventing visualization of the pancreas and no simple and reliable method of reducing its quantity has yet been described (Meire and Farrant, 1978). Repeat scans after a short interval will, however, yield success in 40–50% of these patients; and since ultrasound is painless and harmless, further repeats can be done on those in whom success is not forthcoming on the initial repeat. We have also occasionally found that the troublesome gas may be fairly well localized and thus scanning from further down the abdomen with 20–30° cranial angulation of the scanning frame, or occasionally further up with caudal angulation, may help to avoid it.

Despite all these manoeuvres, the tail will almost never be seen in its entirety on anterior scans and one must usually be content with visualization of 60–70% of the pancreatic volume. We have had limited success with the posterior approach to the tail though Haber *et al.* (1976), claim 86% success, whilst Doust and Pearce, (1976), on the other hand, maintain that "the normal pancreas is difficult to demonstrate in this view". Fortunately, failure to display the tail seldom leads to a failed diagnosis since inflammatory disease of the pancreas almost invariably also affects the head and body, and the large majority of carcinomata occur in the head. Carcinoma may occur in the tail, however, and more commonly an inflammatory pseudocyst may arise in the left half of the pancreas. Our experience of both these findings is limited, but the posterior approach would be expected to detect lesions of about 4 cm diameter reliably.

Grey scale ultrasound scanning of the pancreas is in its infancy and in the near future improvements in technique and equipment may well make ultrasound the primary definitive procedure for pancreatic investigation.

The advent of real-time scanners has certainly greatly eased the task of locating the pancreas, but the still images obtained from these devices lack much of the detail seen on conventional scanners. Whilst we do not feel that real-time scanners are adequate for pancreatic diagnosis at the present time, the improving image quality does now permit

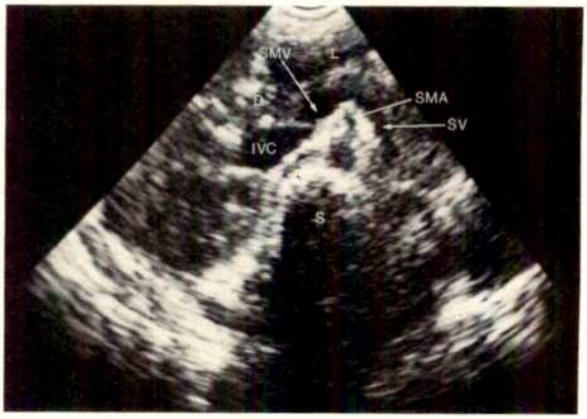

FIG. 12.

Single frame from a real time scanner (Nuclear Enterprises 4260 "Spinner") (compare with Fig. 7). D duodenum; IVC inferior vena cava; L liver; S spine; SMA superior mesenteric artery; SMV superior mesenteric vein; SV splenic vein.

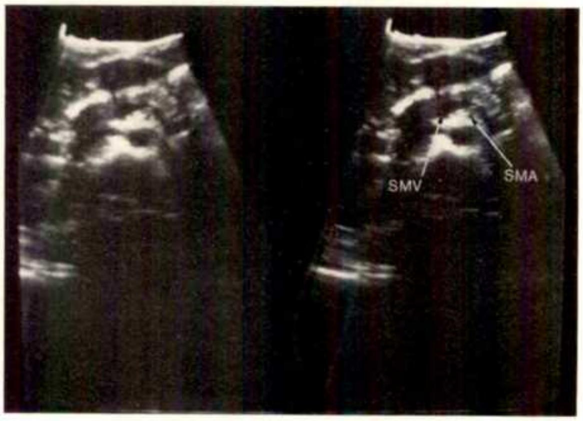

FIG. 13.

A "stereo pair" from the Sonicaid 3D scanner (compare with Fig. 7). SMA superior mesenteric artery; SMV superior mesenteric vein.

recognition of the pancreas and its vascular relations (Fig. 12).

A further recent development in ultrasound imaging, which may have a role to play in pancreatic diagnosis, is the use of stereo pairs of images to permit three dimensional viewing of a chosen tissue volume. Figure 13 is a stereo image of a series of transverse scans of the pancreas, which, when viewed stereoscopically will give a three dimensional effect. The diagnostic potential of this technique is still under evaluation.

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Book review

Practical Abdominal Ultrasound. By Constantine Metreweli, pp. ix+121 Illus., 1978 (Heinemann Medical, London) £12·50.
ISBN 0–433–21311–6

"This book is written by a beginner for beginners" (Preface) summarizes the value and implies the limitations of this excellent introductory book. Diagnostic ultrasound is a practical subject, undoubtedly best learned by an apprenticeship, but here is a logically ordered text that takes the beginner by the hand and literally instructs which control to manipulate to improve which imperfections in a scan. There is an illustrated chapter on elementary but pertinent physics (no maths!) and a lucid explanation of spurious images ("artefacts"). The beginner is then taken progressively through basic obstetrics and on to gynaecology and general abdominal scanning techniques, each question being provided with a list of pathologies likely to be encountered and a catalogue of ultrasound findings. The latter is illustrated with clear diagrams supplemented by a set of ultrasound plates for each chapter. These are of good quality, though necessarily rather brief. The lists also tend to be so compressed as sometimes to degenerate into telegraphic headings without explanation in some of the later chapters but nevertheless they form a useful reminder of conditions the sonographer should bear in mind. There is also a useful set of obstetrical tables and throughout the book realistic measures of the dimensions of organs and vessels are included.

Inevitably with such a down-to-earth, practical approach, it has not been possible to provide advice applicable to all types of scanner, and cine-ultrasound (real-time) systems have only been mentioned. In fact the machine controls detailed apply specifically to the Emisonic (Diasonograph) static scanners of the 4200 series, which have some peculiarities of electronic and mechanical design that set them apart in a class of their own. The intelligent user will be able to modify the instructions for use with the scanner at hand and this specialization in the text is not a barrier to the general use of the book.

The compressed nature of the clinical sections carries a distinct risk of over-simplification and the unwary user might be surprised at the degree of normal variation he will encounter and be beguiled into expecting pathology always to comply with the appearances illustrated. In addition to the limitations inherent in the simplification proper to a "beginners" book, there are a few outright errors, mostly affecting the illustrations. For example the caudate lobe of the liver is here, as in other worthy texts, repeatedly mislabelled, and there is obvious internal inconsistency. For the record the central figure of page 66 is correct; in others the lobe called "caudate" is the medial portion of the right lobe of the liver. In another diagram (Fig. 14.3) Riedels lobe has mysteriously become displaced to form an extension of the left lobe instead of the right lobe of the liver.

These are relatively minor points and this book can be warmly recommended as a realistic, practical manual for the beginner in diagnostic ultrasound with special reference to the Emisonic 4200 series scanner.

David O. Cosgrove.

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Total-body irradiation in advanced lymphosarcoma

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ABSTRACT

Thirty patients with stage III and IV non-Hodgkin's lymphoma were treated by total-body irradiation (TBI). Eleven patients had previously received local radiotherapy or chemotherapy. Toxicity was confined to haematological depression. Complete remission of disease was achieved in 14 patients. Non-leukaemic patients who had received no previous treatment reacted best to TBI (ten complete remissions in 13 patients). We consider TBI a helpful treatment in non-leukaemic patients with advanced lymphosarcoma.

In view of the favourable results of preliminary experience with total-body irradiation (TBI) in the management of advanced lymphosarcoma reported by others (Johnson and Ruhl, 1976; Chaffey *et al.*, 1975), a pilot study was initiated at the Department of Radiotherapy of the University of Utrecht in January 1976. This record summarizes our observation on 30 patients.

MATERIAL AND METHODS

Thirty patients with generalized lymphoma were entered into the study. Eleven patients had previously received local radiotherapy or chemotherapy, while 19 patients had received no previous therapy (Table I).

The original diagnostic lymph-node biopsies were reviewed and classified according to the Rappaport classification (Rappaport, 1966) of non-Hodgkin's lymphoma's (Table II). Staging was according to the Ann Arbor system (Carbone *et al.*, 1971). The 30 patients accepted were either stage III (six patients) or stage IV (24 patients) as determined by clinical examination, chest radiograph, lymphangiogram (in nearly all cases), bone marrow biopsy and biochemical tests. Some patients had laparotomies. The age and sex distribution is shown in Table III.

The patients were treated in a standing position with a 6 MeV linear accelerator at a distance of 600 cm from target to skin. The course of TBI consisted of 10 rad mid-plane fractions three times a week to a maximal total dose of 300 rad.

TABLE I

PATIENTS

30 patients	19 no previous treatment	
	11 after previous treatments	4 radiotherapy 6 chemotherapy 1 both

TABLE II

HISTOLOGICAL SUBCLASSIFICATION (RAPPAPORT, 1966)

	Diffuse	Nodular
Well differentiated lymphocytic	3	1
Poorly differentiated lymphocytic	12	11
Undifferentiated histiocytic	1	
Mixed lymphocytic – histiocytic		1
Mixed histiocytic – immunoblastic	1	

TOXICITY

Except for haematological depression TBI was tolerated without significant immediate morbidity by all patients. Vomiting, diarrhoea, skin changes and alopecia were not observed. Those patients with disease-related symptoms often experienced a marked clinical improvement with remission of disease even while undergoing treatment.

Haematological depression was, however, induced in most patients (Tables IV and V). Sometimes it was moderate in degree (leucocytes not below $2 \times 10^9/l$ and thrombocytes $30–100 \times 10^9/l$ without spontaneous bleeding) and transient in nature. However, profound bone-marrow depression during and after radiotherapy was observed several times.

Our overall impression of haematological depression caused by TBI is that it is generally acceptable and if necessary can be satisfactorily treated. In some patients, however, it was unpredictable (by bone marrow involvement) and very severe. In patients who had received previous treatment more risks have to be taken because of failure of the other treatment.

TABLE III

AGE AND SEX DISTRIBUTION

Age	21–40	41–60	61–79	total
Male	4	5	6	15
Female	–	6	9	15

TABLE IV

RESULTS IN 19 PATIENTS WITH NO PREVIOUS TREATMENT

Bone marrow involvement	Toxity	Results
No bone marrow involvement (7)	2 no toxicity 4 mild platelet fall 1 pancytopenia	complete remission complete remission complete remission no remission – chemotherapy complete remission complete remission complete remission
With bone marrow involvement (6)	3 mild platelet fall 2 pancytopenia 1 no evaluation	complete remission complete remission death of other disease before evaluation complete remission partial remission refused further treatment
Leaukemia (6)	5 leukaemia 1 no toxicity	no remission – remained leukaemic complete remission

TABLE V

RESULTS IN 11 PATIENTS WHO HAD RECEIVED PREVIOUS TREATMENT

Bone marrow involvement	Toxicity	Results
No bone marrow involvement (6)	1 no toxicity 3 mild platelet fall 1 pancytopenia 1 lethal pancytopenia	complete remission incomplete remission – chemotherapy complete remission complete remission complete remission no remission
With bone marrow involvement (2)	persisting pre-existent pancytopenia	insufficient dose reached no remissions
Leukaemia (3)	leukaemia	insufficient dose reached no remissions

RESULTS

We define complete remission as total disappearance of clinical, radiographic and laboratory (including bone marrow) evidence of disease, together with resolution of related symptoms, for a minimum of two months. In our group the highest response rate was obtained in patients who had received no previous treatment (Table IV). The results in the other patients are shown in Table V. The response of the patients who reached complete remission is shown in Figs. 1 and 2.

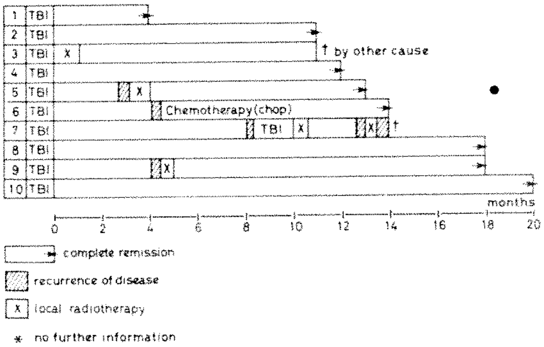

FIG. 1.

Follow-up of 10 patients with complete remissions and no previous treatment.

DISCUSSION

For many years chemotherapy has been the primary modality of treatment for patients with advanced stages of lymphosarcoma. Assessment of the value of TBI as opposed to polychemotherapy as the primary treatment in patients with disseminated lymphosarcoma would require a large prospectively randomized clinical trial, but some conclusions may be drawn from our pilot study. The analysis of results of polychemotherapy shows that about 40%

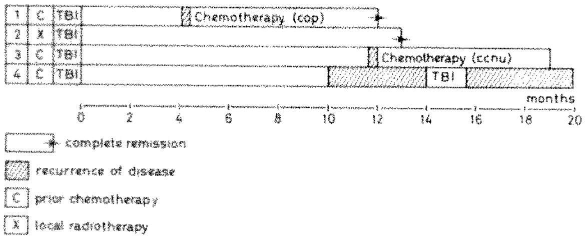

FIG. 2.

Follow-up of 4 patients with complete remissions after TBI and previous treatment.

of patients achieve a complete remission (DeVita *et al.*, 1975) It is well known that detailed features of lymph-node histology have prognostic significance for survival in patients treated with chemotherapy. We do not know yet if histology has the same prognostic value in patients treated by TBI.

In our group of patients we have reached more than 40% complete remissions in patients who had received no previous treatment (ten out of 19 patients, 53%). This is particularly encouraging since in our study there is a large number of patients with poor pathology. Results in patients with leukaemia treated by TBI are very poor. We do not intend to go on treating these patients. In non-leukaemic patients with no previous treatment we reached ten complete remissions out of 13 patients (77%)

TBI is a very well tolerated treatment as compared to chemotherapy. TBI is a simple method of treating patients and it is not associated with troublesome side effects. Haematological toxicity may be severe but in non-leukaemic patients it is in general acceptable. In our opinion it is an important point to remember that TBI was also helpful in those non-leukaemic patients who had already exhausted all other forms of therapy. TBI therefore may be applied if chemotherapy does not give full remission. We do prefer, however, to give TBI as the primary treatment to patients with advanced stages of lymphosarcoma. If TBI does not result in complete remission, however, haematological depression does not generally exclude chemotherapy after TBI. We therefore conclude that TBI is a helpful treatment in the management of advanced lymphosarcoma.

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Book review

Craniotomography. An atlas and guide. By Klaus Reisner and Gochen Gosepath with co-operation of R. Hülse, pp. 196, illus., 1977 (Georg Thieme Publishers, Stuttgart), £31·25.

This book discusses and illustrates the value of multidirectional tomography in the examination of the human skull.

It commences with a clear account of the problems of technique, demonstrating the limitations of the tomographic method and establishing the superiority of multidirectional over other types of movement in the examination of the skull.

Chapters on normal tomographic anatomy and selection of projections for showing various structures are followed by consideration of pathology by regions, with chapters on the nasopharynx, paranasal sinuses, orbit, base of skull, temporo-mandibular joint and mandible and the temporal bone. The final chapter discusses tomography in head injury.

In each region and with each condition the relevant features of the pathology, pathological anatomy and the place of tomography as well as the findings are clearly analysed.

The book is extensively illustrated with diagrams and beautifully reproduced tomograms, most of which are accompanied by labelled and exactly comparable line drawings. There is a good selection of references, which has been brought up to date for the English translation of the original German edition.

It is a well written, lucid text, which takes the reader in a simple and logical fashion through many complex conditions. It is strongly recommended as a text book for anyone commencing study of the subject, but it also contains original material and reviews the literature in a way that make it valuable for reference.

B. KENDALL.

1979, *British Journal of Radiology*, *52*, 571–572 JULY 1979

NSD and cell survival

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(Received May, 1978 and in revised form November, 1978)

ABSTRACT

The relation between the NSD concept and cell survival in fractionated irradiation is established; the slope of Strandquist's lines is related to the shape of survival curves for the given type of cells and radiation. A new parameter, CBE, derived from TDF for determining cumulative biological effect is proposed.

The introduction of the NSD concept (Ellis 1967) for evaluation of tolerance irradiation conditions has been a very important step which has brought a more exact element into empirical radiotherapy. This approach has continued by the introduction of similar quantities—CRE, TDF—for evaluation of radiation effects at subtolerance levels (Kirk *et al.*, 1971; Orton and Ellis, 1973). Today it is especially the TDF factor with its additive properties which is made use of in many radiotherapy departments.

However, all the above mentioned quantities are still lacking to a certain extent. They express the level of radiation effect in a scale whose relation to the cell-survival fraction is unknown. There exist of course some other attempts which try to determine the surviving fraction of cells at the end of a fractionated course of treatment. They combine the survival curves from single doses with the effect of proliferation in the intervals between the individual fractions (Cohen and Redpath, 1977). As very little is known about proliferation the mathematical approach used seems to be still rather arbitrary and one cannot be at all sure that it corresponds to an actual situation.

Thus the linear behaviour of Strandquist's graphs seems to be the only fact which is now established reasonably reliably. In our view progress can be maintained only if at least some approximate relation can be established between the NSD or related factors and the actual biological scale expressed in cell survival. It will be shown in the following that such a relation has actually been found. At the same time a new parameter, CBE, has been introduced, determining the cumulative biological effect, which is merely a multiple of TDF and has, therefore, the same additive properties. It is a dimensionless quantity, which enables the survival fraction at the end of any fractionation course to be established in a simple way.

TDF FACTOR AND THE SURVIVAL FRACTION

We start from the usual expression

$$\mathrm{TDF} = \mathrm{N}\mathrm{d}^{\gamma}\,\mathrm{t}^{-\beta} \quad . \; . \; . \; . \; . \; (1)$$

where

$$\gamma = \frac{1}{1-\chi} \quad . \; . \; . \; . \; . \; . \; (2a)$$

and

$$\beta = \tau\gamma \quad . \; . \; . \; . \; . \; . \; (2b)$$

and N is the number of fractions.

χ is the slope of Strandquist's line equating

$$\chi = \upsilon + \tau.$$

The parameters υ and τ are the known exponents introduced by Ellis; we use the general symbols to allow for the fact that the slope of Strandquist's graphs can differ for different types of tissues and radiations (see for example Wara *et al.*, 1973; Field *et al.*, 1976).

TDF is additive. Therefore,

$$\mathrm{TDF} = \sum_{i=1}^{N} (\mathrm{TDF})_i \quad . \; . \; . \; . \; (3)$$

The surviving fraction of cells at the end of a fractionation course of irradiation may be given by the following general expression, assuming full recovery between fractions

$$\mathrm{S_N(D,T)} = \prod_{i=1}^{N} \mathrm{S_i(d,t)}. \quad . \; . \; . \; . \; (4)$$

or

$$\ln \mathrm{S_N(D,T)} = \sum_{i=1}^{N} \ln \mathrm{S_i(d,t)} \quad . \; . \; . \; (5)$$

where $S_i(d,t)$ is the cell survival following the i-th fraction.

As Eqs. (3) and (5) which express the same effect have an identical form, one can come at once to the conclusion that

$$\ln S_i(d,t) = \alpha\,(\mathrm{TDF})_i$$

or

$$S_i(d,t) = S(d,t) = \exp(-\alpha d^{\gamma} t^{\beta}) \;.\;.\;.\;(6)$$

where α is a constant. If we insert for v and τ the values given by Ellis, we obtain

$$S(d,t) = \exp(-\alpha d^{1.538}\, t^{-0.169}) \text{ for normal tissue,}$$
$$.\;(7)$$
$$S(d,t) = \exp(-\alpha d^{1.315}) \text{ for tumour.}$$

It has been shown by Hugget (1976) that expressions of the type

$$s(d) = \exp(-\alpha d^{\gamma}) \;.\;.\;.\;.\;.\;(8)$$

can be used well for the description of survival curves; *e.g.*

$\gamma = 1{,}52$, $\alpha = 8{,}0$
or $\gamma = 1{,}48$, $\alpha = 5{,}49$ for some aerobic cells,
$\gamma = 1{,}36$, $\alpha = 1{,}66$ for some hypoxic cells,

if the dose is measured in krad. The parameter γ is in quite good agreement with the numerical values derived from Ellis' parameters (see Eq. (7)).

A NEW PARAMETER FOR CUMULATIVE BIOLOGICAL EFFECT

If the parameters v and τ are not constant and differ for different types of tissues and radiations, the numerical values of CRE and TDF cannot be used for a comparison of biological effect in a general case. It seems, therefore, suitable to introduce a further parameter derived from TDF by

$$\mathrm{CBE} = \alpha\,\mathrm{TDF} \;.\;.\;.\;.\;.\;.\;(9)$$

which determines the cumulative biological effect in any general case if the parameters α, v, τ correspond to the given tissue and to the given irradiation conditions. The surviving fraction at the end of a fractionation course is then equal to

$$S_N(D,T) = e^{-\mathrm{CBE}} \;.\;.\;.\;.\;.\;(10)$$

The parameter α equals $\alpha = \alpha_d \cdot \alpha_t$, where α_d can be determined from survival curves; α_t relates to proliferation processes and must be determined from experimental data with fractionation.

TABLE I

THE RELATION BETWEEN THE CBE AND THE FRACTION OF DESTROYED CELLS

CBE	1	3	5	8	10
(1 − S) [%]	63.2	95.0	99.33	99.97	99.995

The parameter CBE has the same additive properties as the TDF factor. Its further advantage consists in the fact that it is a dimensionless quantity, having a direct relation to the cell survival—see Eq. (10); the corresponding values are given in Table I. The value of CBE can be used in the future as a new criterion for evaluation of any therapeutic fractionation scheme. Its value for normal cells should be as low as possible while keeping that for tumour cells sufficiently high.

The fact that CBE can be expressed with the help of the parameters γ and α_d gives a new method of analysing the influence of radioprotective or radiosensitive agents, and their use in improving fractionated radiotherapeutic schedules.

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1979, *British Journal of Radiology*, *52*, 573–574 JULY 1979

Technical notes

A proposed afterloading technique for irradiation of the oesophagus

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(*Received December 1978*)

The aim of any radiotherapy for oesophageal tumours would be to cure or at least to offer relief from dysphagia or obstruction with the minimum of discomfort to the patient and with the minimum of damage to the surrounding tissues and organs. It is well known that early attempts at intracavitary therapy of the oesophagus, alone or as a supplement to external X-ray therapy, have not been particularly successful. The reasons for this are as follows: (a) if the applicator consists of a radioactive source inside a narrow catheter, then insertion into the oesophagus is possible even with strictures present. However, the necessarily short treatment distance results in poor dose distribution within the treatment volume. (b) If the applicator is of larger diameter to obtain an acceptable dose distribution, the advantage is liable to be lost as a result of the definite hazards linked with the insertion of a wide solid-type applicator.

If there is residual tumour following conventional external beam therapy, it is not practicable to attempt any further regression by continually increasing the tumour dose, since the safe dose limit to the areas in close proximity, such as the spinal cord or lungs, would be exceeded. However, a system is now proposed whereby the tumour dose can be increased without adding significantly to the dose to the cord, for example, and at the same time substantially reducing the problems specified in (a) and (b) above. Following a course of external radiotherapy, further fractionated therapy using iridium 192 ($t_{\frac{1}{2}}=74$ days 0.30–0.61 MeV γ rays) wire is proposed. This treatment can be radical or palliative and the technique combines the advantages of low catheter diameter during insertion and, subsequently, a constant treatment distance sufficient to give an adequate dose distribution.

The intracavitary device and its catheter cross-sections are shown schematically in Fig. 1. The central lumen can accommodate the wire source, a spacer and a trocar for insertion. The remaining lumens permit air to pressurize the outer large balloon which would be approximately 10 cm in length and, independently, the small inner balloon. The balloon joints are pressure tight and the balloon thickness a compromise between adequate expansion sensitivity and the avoidance of non-cylindrical expansion. This outer balloon can thus be inflated under carefully controlled pressurizing conditions to a safe pressure level within the oesophagus to secure a cylinder of diameter approximately 2 cm. The inner balloon, separately inflated, serves to maintain a central position of the wire and also to help, through application of pressure, to dilate any stricture in the residual tumour. The catheter should be narrow to facilitate easy passage through any stricture. A final diameter of approximately 6 mm is considered practicable following investigations into the manufacturing process. The smoothly tapered stainless steel pilot at the end of the catheter should be a tight push fit and serves to ease introduction of the catheter even more and also to allow removal of the wire source after use. If the balloons are partially radio opaque, radiological screening of the positioning of the device is possible and allows also the treatment distance to be calculated.

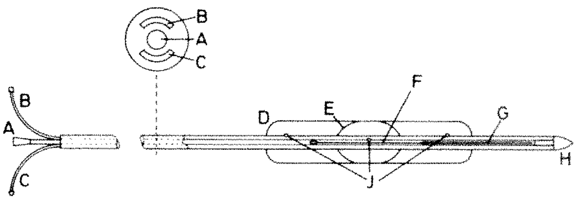

FIG. 1.

Schematic diagrams of longitudinal and transverse cross-sections of oesophageal catheter. Lumens A, B and C for iridium wire F and balloons E and D, respectively Spacer G. Pilot H. Inflation ports J.

The length of the source and the distance from the tip of the source to the tip of the catheter are predetermined from radiographic information. The non-loaded catheter is carefully passed down the oesophagus until the centre of the inner balloon lies midway between the treatment boundaries. When viewed using screening techniques this balloon is

1979, *British Journal of Radiology*, 52, 574–576

then slowly pressurized under controlled conditions to distend the oesophageal lumen to an acceptable limit. The main balloon, whose pressure can be monitored, can then be inflated at a monitored pressure slightly greater than the external atmospheric pressure, using an air cylinder whose capacity is many times that of the balloon when inflated. When the clinically acceptable diameter is obtained the supply tap can be closed and the cylinder pressure then equalized via a relief valve to that of the main balloon. On opening this tap the cylinder will then act as a pressure sink and would help to sustain the diameter in the unlikely event of a small air leak. To render the device safe a Hi/Lo pressure switch can be incorporated, to operate a solenoid relief valve should the safe pressure level be accidentally exceeded, and to operate an alarm in the event of deflation.

The spacer can then be loaded into the central lumen followed by the linear source and pushed down with a flexible trocar which can then be clamped in position. The only information required for the choice of source strength is the tumour length, treatment distance and dose at that given treatment distance. A computer program based on the work of Vickery and Redpath (1977) has been written to calculate the mean dose rate at the required distance from the line source of given activity and to calculate the optimum differential loading arrangement. The treatment time pertaining to the geometrical circumstances as indicated by the screening techniques can then be calculated for that particular patient.

Radioactive iridium wire 0.6 mm diameter is available to give dose rates in excess of 500 rad/h for a treatment distance of 1 cm and differential loading is achieved by doubling over each tip by a computed extent. An alternative would be to employ a commercial remote after-loading apparatus using either high or low activity cobalt pellets. A literature search has revealed that a method embodying similar principles has been adopted (Abe *et al.*, 1976), the short insertion times of approximately 90 seconds per fraction being achieved using high activity ^{60}Co pellets. Recent information (T. Mizoe, private communication) has suggested that low dose rates, with longer insertion times for each fraction, may be clinically more effective.

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Radiotherapy planning of inclined lesions

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The angulation of radiotherapy machines to treat inclined lesions was first described by Besford *et al.* (1964). A detailed mathematical analysis of the general case of an inclined lesion was carried out by Fleming and Orchard (1974), and their theory applied to two specific treatment techniques by Casebow (1976). These two techniques were: "Method 1" – Treatment plane perpendicular to the lesion axis, and "Method 2" – Treatment plane vertical and perpendicular to the patient axis.

The aim of this note is to derive the relevant equations for a third technique which offers some practical advantages over the other two methods, and to consider the effect of angulation on the focal – skin distance along the length of the lesion. This method uses a treatment plane which is vertical and perpendicular to the projection of the lesion axis onto a horizontal plane.

Theory

In general, the long axis of the lesion, *l*, will be as shown in Fig. 1a. The co-ordinate system which provides a frame of reference is orientated so that *k* is vertical and *j* is parallel to the horizontal rotation axis of the radiotherapy machine; the patient's sagittal plane is parallel to the *j*, *k* plane. Fig. 1b also shows the projection of the lesion onto the *i*, *j* plane (as it would appear in an AP radiograph) and Fig. 1c the *j*, *k* plane (lateral radiograph).

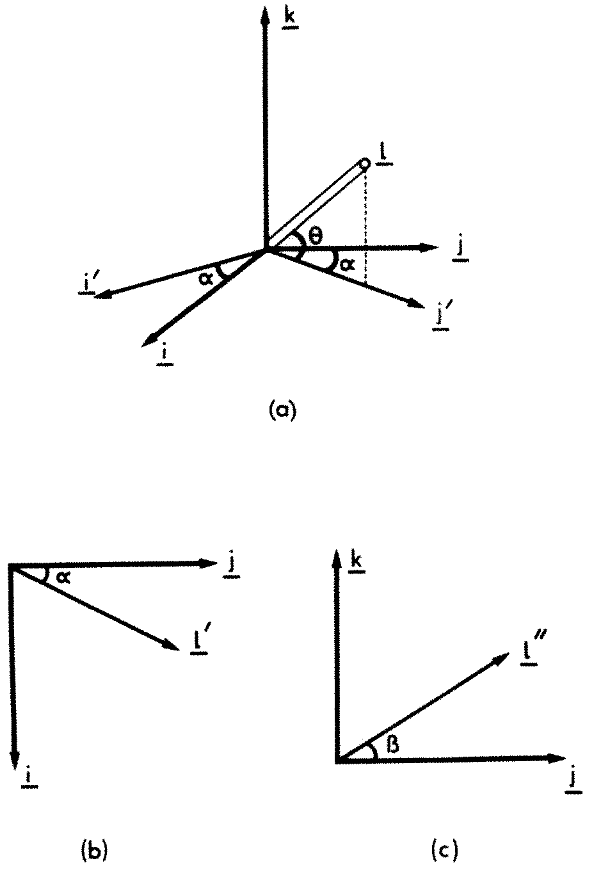

FIG. 1.

(a) The central axis of the lesion, l, in relation to the co-ordinate system.
(b) Its projection onto the i, j plane, as in an AP radiograph.
(c) Its projection onto the j, k plane, as in a lateral radiograph.

Calculation of lesion angle to the horizontal

From Fig. 1, the true angle of the lesion to the horizontal, θ, is given by

$$\tan\theta = \tan\beta \cos\alpha \quad . \quad . \quad . \quad . \quad (1)$$

Calculation of diaphragm rotation angle

It is convenient to use the transformed co-ordinate i', j', k achieved by rotating the treatment couch through an angle α. This ensures that the treatment plane is perpendicular to the projection of the lesion axis onto a horizontal plane. The necessary rotation of the diaphragm about the beam axis, ϕ, differs from θ as shown in Fig. 2, and is given by

$$\tan\phi = \tan\theta . \sin\gamma \quad . \quad . \quad . \quad (2)$$

where γ is the angle of the beam axis from the vertical, *i.e.* the arc angle.

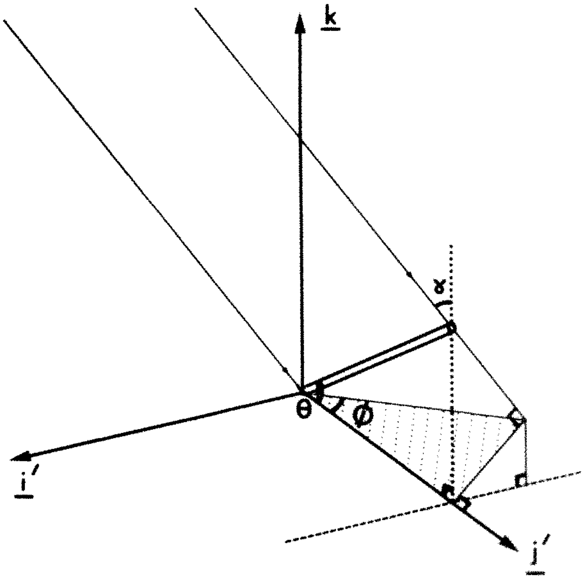

FIG. 2.

The diaphragm rotation angle ϕ varies with both θ and γ.

Calculation of true lesion length

The true length of the lesion, l, may be calculated from the apparent length (corrected for film magnification) in either the AP or lateral radiograph. From Fig. 1

$$l = \frac{l'}{\cos\theta} = l'' . \frac{\sin\beta}{\sin\theta} \quad . \quad . \quad . \quad . \quad (3)$$

where l' and l'' are the apparent lesion lengths in the AP and lateral radiographs respectively.

Calculation of angle between beam axis and lesion

In general, the central axis of the radiation field or "field axis", f, will not be perpendicular to the lesion axis, l. Let the angle between them be ψ, as shown in Fig. 3.

$$\text{From Fig. 3, } \cos\psi = \sin\theta . \cos\gamma \quad . \quad . \quad (4)$$

As the angle between l and f usually differs from 90 deg., the distance from the radiation source to the lesion mid-line will vary along the length of the treatment volume, as shown in Fig. 4. This in turn will affect the dose rate along the mid-line, and must be taken into account in the treatment planning. If d is the distance from the radiation source to the lesion mid-line, measured along the central axis of the field, then the corresponding distances, d' and d'', at either end of the lesion are given by:

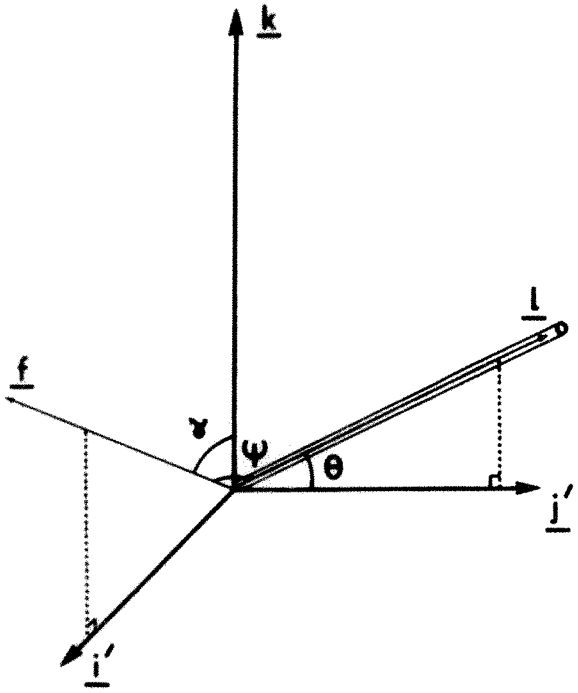

FIG. 3.
The field axis is no longer perpendicular to the inclined lesion.

$$\left.\begin{aligned} d' &= d + \frac{l}{2}\cos\psi \\ d'' &= d - \frac{l}{2}\cos\psi \end{aligned}\right\} \quad . \quad . \quad . \quad (5)$$

DISCUSSION

The method proposed is simple to use in practice, and is applicable to a typical oesophagus treatment consisting of an anterior field and two posterior oblique fields. First, the true angle of the lesion to the horizontal, θ, is calculated from the apparent angles α and β measured on the AP and lateral radiographs respectively using equation 1. The couch rotation angle α is obtained directly from the AP radiograph; this rotation achieves the desired transformation of co-ordinates. Next, the diaphragm rotation angle, ϕ is obtained from equation 2. Note that the magnitude of ϕ is the same for arc angles γ and $-\gamma$, only the sign changes.

After the true length of the lesion has been calculated from equation 3, the angle between the field and tumour axis is obtained from equation 4. This inclination leads to a changing distance from the tumour axis to the radiation source, a point not explicitly considered by other authors. Equation 5 is used to calculate this distance at each end of the lesion so that corrections may be made to the dose rate. This enables the dose to be calculated at any point on the mid-line of the lesion where a contour is available. Usually, three contours are sufficient to assess the variation of dose and allow calculation of any required compensation.

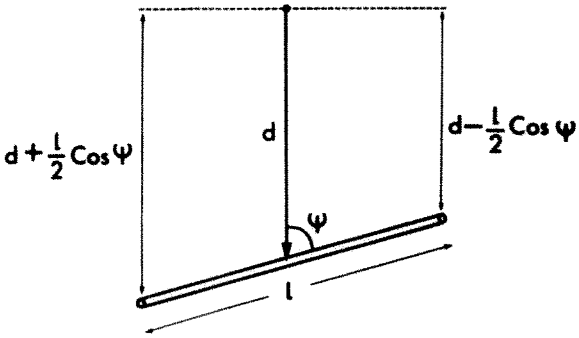

FIG. 4.
The distance from the radiation source to the lesion mid-line varies along the length of the treatment volume.

Compared with the techniques described by Casebow (1976) this method has the advantage of simplicity without loss of accuracy. This technique enables the rotation angle of the couch to be obtained directly from the AP radiograph without modification, an advantage when a simulator is being used. Since the diaphragm rotation angle ϕ is the same for both posterior oblique fields (except for a change in sign), this eliminates one possible error in the patient set-up. This is in contrast to the second technique described by Casebow (1976) which requires different diaphragm rotations for each field. The other method of Casebow (1976) simplifies the calculation of dose, but the restriction on arc angle necessary to make the treatment plane (*i.e.* the plane formed by the central axis of the three fields) perpendicular to the lesion axis may produce an inferior treatment plan. Certain combinations of arc angle and couch rotation may be impossible with a particular machine, but the technique described here has been found to work well in practice for the vast majority of cases.

ACKNOWLEDGMENT

I would like to thank Dr. J. Kirk of this department for helpful discussion.

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July 1979

Technical notes

A comparison of two hard-copy display systems for nuclear medicine images

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We recently changed our method of hard-copy display of nuclear medicine images from a system based upon the use of Polaroid film to one employing 20 × 25 cm X-ray film. Although our subjective impression indicated an improvement in image quality, we also sought some objective means of assessing whether there was an improvement in detectability of lesions.

The requirements of a film for nuclear medicine imaging were discussed by Merrigan *et al.* (1977). A comparison of four different films was undertaken by Henry *et al.* (1973) who based their conclusions on clinical impressions and the reliability of each system. The present communication presents the results of assessing one hundred brain scans using a method described by Houston and Macleod (1977). It should be emphasized that the present work set out to compare two display systems and is not a direct comparison between Polaroid and X-ray film as a display medium.

METHOD

Houston (1977) has produced from departmental records a series of one hundred normal brain scans, one view per normal patient, obtained with a Nuclear Chicago (Searle) Pho Gamma III camera with a high resolution collimator interfaced to a Varian 620/L-100 minicomputer. Fifty "tumours" were added mathematically at selected positions to scintigrams in this series, no more than one to a view. These scans were transferred to a disk on our DEC PDP8/E minicomputer via 8-track paper tape.

The purpose of this investigation was simply to assess whether the change from a display system using Polaroid film as the hard copy to one employing X-ray film had produced a significant improvement in detectability. To this end, each scintigram was enhanced using an "unsharp masking" filter (Corfield, 1976) and displayed on both media as in routine practice.

Each image was displayed in core as a 64 × 64 matrix array with eight grey-scale levels. Images on Polaroid film (type 107) were obtained using a Shackman camera coupled to a slave video monitor. The images were also displayed on a point-plot display (a short persistence Hewlett-Packard 1332A CRT) and imaged onto 20 × 25 cm X-ray film (Kodak Xomat XL1) by means of a Picker folded optics camera incorporating a × 2.5 magnification enlarging lens (Corfield *et al.*, 1978). An example of each display is shown in Fig. 1.

The displays were then presented to a clinician, a scanning technician and two physicists, all experienced in nuclear medicine. Each participant was

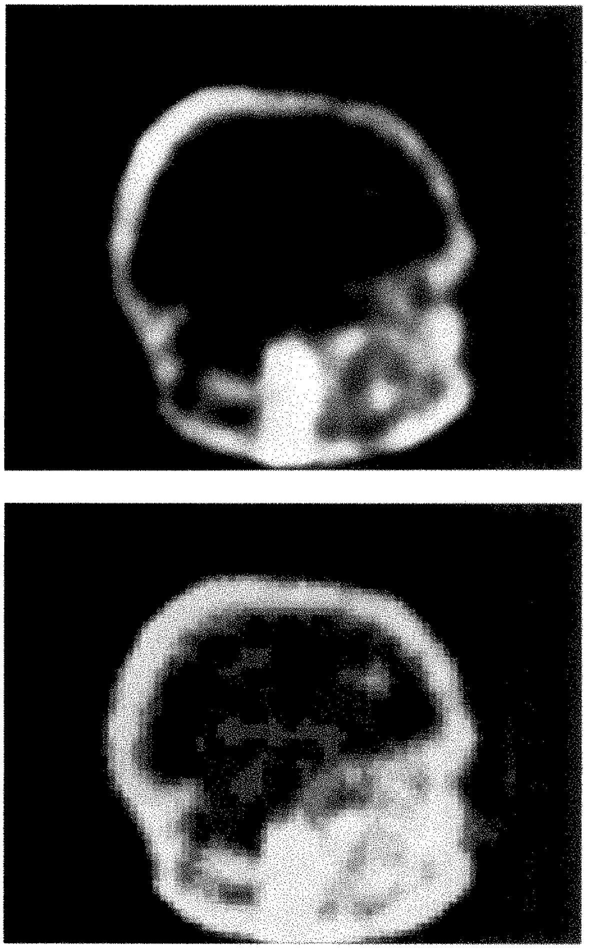

Fig. 1.

An image of one of the computer-processed brain scans used in the intercomparison of X-ray film and Polaroid film. X-ray above, Polaroid below.

informed that no more than one tumour was present in any view and that the probability of an abnormal was 0.5. The order of presentation of each set, *i.e.* Polaroid or X-ray film, was varied. Each participant was then asked to rate the views using the five-scale category suggested by Goodenough *et al.* (1974), and to indicate the Cartesian co-ordinate of the suspected lesion. Localization receiver operating characteristic (LROC) curves (Starr *et al.*, 1975) were generated for each set of results together with a points score described by Houston and Macleod (1977). The positional discrepancy allowed was 2 cm or 2½ times the tumour radius, whichever was greater.

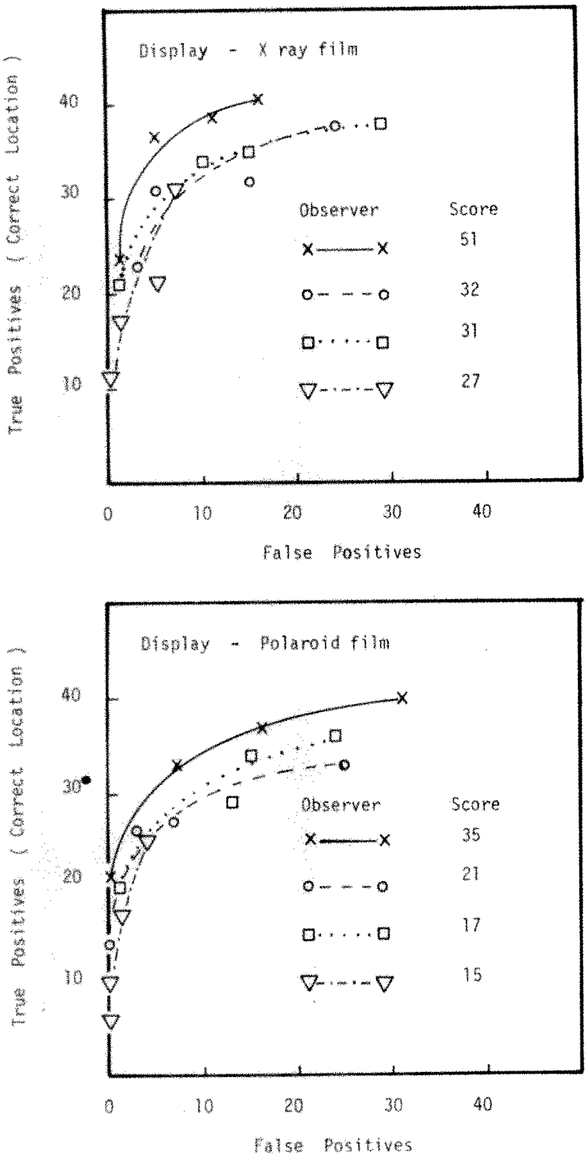

Fig. 2.

LROC curves for the two display systems constructed using the method described by Houston and Macleod (1977).

Results and Discussion

The LROC curves together with the points score for each participant using the two different display systems are shown in Fig. 2. Although the absolute score showed a large variation between observers in each of the two systems it is interesting to note that the ratio of scores between the two systems for each observer was approximately constant (in the range 1.46 to 1.82) irrespective of where the observer set his confidence thresholds. This suggests an increased performance using the new system although it is realized that this approach of evaluating the ratio is not strictly valid.

Criticisms of the approach used here are worth mentioning so that the results obtained by LROC curve analysis should not be over-emphasized. The clinician who took part in the study found it difficult to make an assessment with only one view and with no clinical background. Also the large number of positives used in the study is certainly not representative of what we are used to. Furthermore the use of high-quality modern gamma cameras is tending to eliminate the need for static image processing by currently used data processing systems. Unprocessed analogue images cannot be appraised by the method although it is our belief that these images are better displayed on X-ray film rather than on Polaroid film.

The results presented here are by no means exhaustive although it is feasible to use the same method of analysis with images other than brain scans. However it has increased our belief that changing our display format from a system using Polaroid film to one incorporating X-ray film has been worthwhile, not only because of reduced film cost but also because of an improved standard of image presentation.

Acknowledgment

We should like to thank Dr. A. S. Houston for making available the brain scans and for his critical evaluation of the manuscript.

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Book review

A User's Guide to Diagnostic Ultrasound. By. I. M. Shirley, R. J. Blackwell, G. Cusick, D. J. Farman, and F. R. Vicary, pp. xxi+329, illus., 1978 (Pitman Medical, London), £12·00. ISBN 0-272-79419-8

The material for this user's guide derives from the ultrasound course at University College Hospital, London, and aims to familiarize the newcomer to ultrasound with the essential physical principles and limitations of the technique. It is an excellent example in the presentation of physics for a non-mathematical reader. Not only the basic principles, but complex, though relevant concepts such as the operation of the scan convertor and the effect of various signal compression characteristics on ultrasonic images are explained verbally in lucid fashion with excellent diagrammatic support. It provides a good entrée into the mysteries of ultrasound physics and the workings of all types of scanners currently on the market. As is clearly pointed out in the text, such an understanding is most helpful in persuading the machine to give of its best for any given diagnostic problem and a knowledge of the physics has its practical application in aiding the operator to disentangle the genuine from spurious (artefactual) echo images.

The book's title leads the reader to expect more than a guide to the physical basis of diagnostic ultrasound, although only about one-third of the text is devoted to clinical ultrasound. This of course is disproportionate and inadequate; the authors of these sections could not be expected to give a comprehensive coverage in so short a space but their degree of success is uneven. Obstetrics is divided into elementary and advanced sections. Each is highly practical and the description on how to measure fetal maturity by a BPD is especially well written. More complex diagnoses are discussed and illustrated, although it is sad to see the safe procedure of amniocentesis done under ultrasound control rendered less safe by the suggestion that it can be carried out in the obstetrics ward according to ultrasonic directions. The degree of uterine rotation with posture and bladder filling can be surprising! The section on ultrasound in gynaecology, though brief, is accurate but the findings in the upper abdomen are treated so superficially as to be a real barrier to a learner. For example, in the description of pancreatic scanning the crucial relationships of the neck of this organ to the superior mesenteric vessels contains an important error: it is stated that the junction of the superior mesenteric vein and the splenic vein to form the portal vein occurs anterior to the neck of the pancreas whereas in fact the junction is invariably posterior to the neck of the pancreas. Presumably this mistake does not account for the author's admitted difficulty in imaging this organ, since they do not appear to use this landmark to identify this part of the pancreas which is highly regrettable since this is a fundamental step used by all practising ultrasonologists. Perhaps their outmoded use of compound scanning is to blame for their lack of success in pancreatic imaging—single pass scans should be used to give the kind of resolution necessary for clinically useful scanning in the abdomen. In the discussion of the use of ultrasound in jaundice, the bald statement that "dilated intrahepatic ducts are usually well seen" is really of no use whatsoever. The good results obtainable have been achieved by close and systematic observation of established criteria for the diagnosis of duct dilatation and these should have been discussed. A disturbingly sweeping statement occurs in the section on the kidney, that renal cysts are easily detected. It is well known in fact that there is considerable difficulty in deciding whether or not a small (less than 2 cm) lesion is a simple cyst, because of spurious echoes appearing within small fluid areas. The crucial point made by B. B. Goldberg that all the criteria for a cyst must be fulfilled before one can be sure tha tone is not dealing with a partly cystic tumour seems to have been missed. The discussion on the poorly reflective tumour illustrated (Fig. 13.7) clinches this: such a lesion should never be diagnosed as a cyst since it does not show increased through transmission of sound.

A sensible section on toxicity, or rather apparent lack of toxicity of diagnostic ultrasound follows, and then there is a rather less useful discussion on recording systems, spending too much time on focusing problems, too little on exposure and none at all on video recording systems. The calibration of B scanners is duly emphasized and a chapter gives a bird's-eye view of the newer types of scanning systems available including ciné-sonar (real-time) scanners.

As a straightforward account of the physics and instrumentation of diagnostic ultrasound, this book can be warmly recommended as in a class of its own and should be read by all would-be ultrasound diagnosticians. The clinical sections, especially that dealing with the abdomen, cannot be recommended but there are several recent textbooks that give adequate coverage of this area.

David O. Cosgrove.

1979, *British Journal of Radiology*, 52, 580–582

Case reports

The diagnosis of osteo-necrosis in Hodgkin's disease—active disease or infarction?

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In generalized Hodgkin's disease the bone may be involved in 10% of cases, usually with sclerotic lesions. Osteonecrosis associated with previous radiotherapy and/or chemotherapy has been reported by Timothy *et al.* (1978), and these authors pointed out the dangers of confusing the diagnosis with active Hodgkin's disease.

I would like to stress the equal danger of assuming that the radiological changes are due to necrosis, and thereby failing to diagnose active Hodgkin's disease.

Case History

A female aged 18 years presented in October 1969 with a six-month history of enlarged nodes in the right side of the neck and some low back pain. Radiographs of the chest and lumbar spine were normal. A node biopsy showed nodular sclerotic Hodgkin's disease. She was staged IA and was treated with irradiation to the right side of the neck, being given 3000 rad tumour dose in 21 days. She remained well until March 1970, when she developed pain in the left sacroiliac region. Radiographs showed sclerosis of the left sacroiliac joint (Fig. 1). The neutrophil alkaline phosphatase score was raised to 90. It was decided that she must have Hodgkin's disease involving the bone, and the left hemipelvis was thus irradiated, using a pair of parallel and opposed 20 × 16 cm fields with a tumour dose of 3000 rad in ten treatments (daily fractions)—the head of the left femur was included in the field. In August 1970 further backache occurred. Radiographs showed sclerosis of the 5th lumbar vertebra, and the lumbar spine was then irradiated with a direct 14 × 8 cm field to 3000 rad incident dose in ten daily treatments. The right ovary was shielded. The pain was relieved, but in November 1970 she developed new nodes in the right side of the neck, and these were irradiated with a direct field giving 3500 rad incident dose in ten daily treatments on a telecobalt unit. At this stage her hip movements were full and painless.

In August 1971 she married, and at that time started to get alcohol-induced pain in the right knee and thigh. Radiographs suggested some sclerosis of the right femoral shaft (Fig. 2). In December 1971 she became pregnant, and on the 23rd August 1972 a baby was born by Caesarian section, as there was a mass overlying the sacrum which

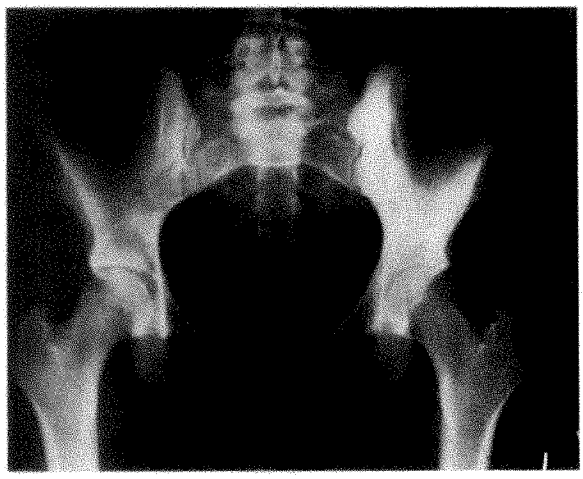

Fig. 1.

Radiograph of pelvis, 1970.

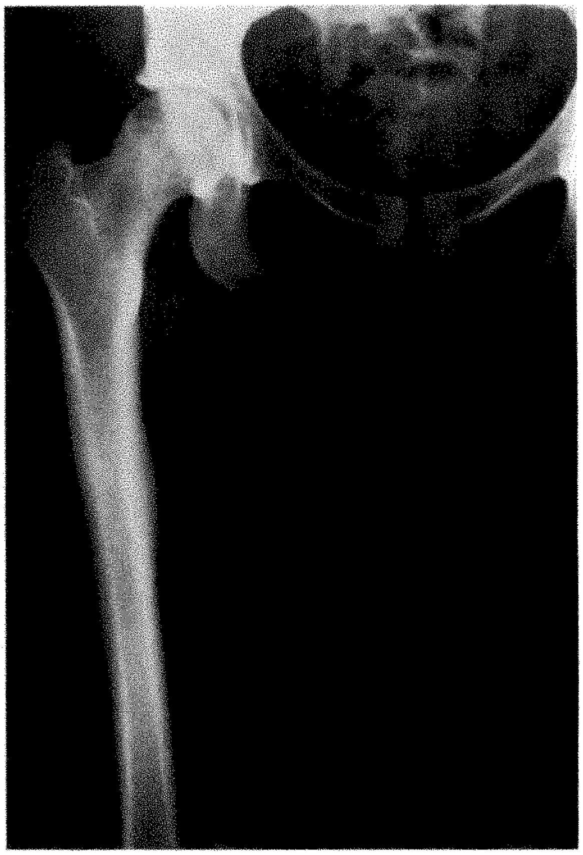

Fig. 2.

Radiograph of right femoral shaft, 1971.

would have prevented normal delivery. At EUA at that time a definite hard mass of tumour was palpable from the sacral brim down to the coccyx. The left ovary was completely atrophic, but the right was normal. One month later a lymphangiogram showed suspicious nodes on the right, at the level of L.4 (Fig. 3), probably involving left para-aortic nodes as well. Irradiation was therefore given to the para-aortic nodes on both sides and to the right side of the pelvis (including the neck of the right femur), but the previously irradiated left side of the pelvis was shielded. She was given a tumour dose of 3000 rad in 15 daily treatments on the telecobalt unit. She rapidly became free of pain and her periods stopped, but she had no flushes and sexual activity was normal.

In February 1973 she was admitted with signs of a pericardial effusion which was thought to be due to Hodgkin's infiltration. Chemotherapy with MOPP (nitrogen mustard, vincristine, prednisone and procarbazine) was started, and over the next 15 months nine courses were given. The pericardial effusion cleared within two months, and she remained free of pain and leading a full and active life. In 1974 radiographs showed early changes in the right femoral head (Fig. 4). In June 1975 pain recurred in the right hip. Radiographs showed increased sclerosis of the neck of the right femur, and it was thought that fracture might occur. There were no other signs of active Hodgkin's disease. The NAP score was 26. She was treated on the 8 MeV linear accelerator, and given a tumour dose of 2500 rad in ten daily treatments (field size 10 × 10 cm). Further bone sclerosis took place, and she became completely free of pain. Since then she has had no further pain in either hip, but she has developed a right-sided limp due to a 5 cm shortening of the right leg. Radiographs in September 1976 showed sclerosis of both upper femora and involvement of the acetabulum.

When last seen on July 28, 1978 she was well and completely free of pain, with no obvious active disease. The blood count, NAP (neutrophil alkaline phosphatase) score and chest radiograph are normal. Both hip movements are markedly reduced, particularly abduction on the right. Radiographs show marked sclerosis of both upper femora (Fig. 5). Her son, aged six years, is completely normal.

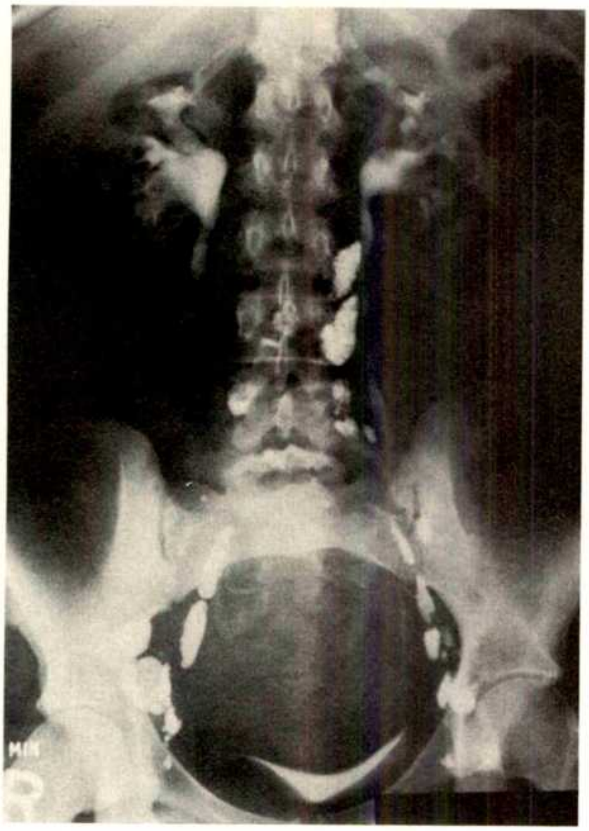

FIG. 3.
Lymphangiogram—suspicious nodes right iliac and left para-aortic regions.

DISCUSSION

Cases of osteonecrosis in both Hodgkin's disease and non-Hodgkin's lymphoma were reported by Ihde and Devita (1975). A further five cases in

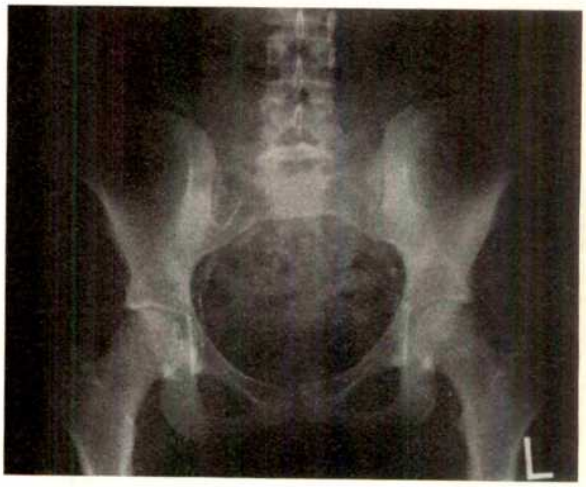

FIG. 4.
Radiograph of pelvis, 1974. Early changes in right femoral head.

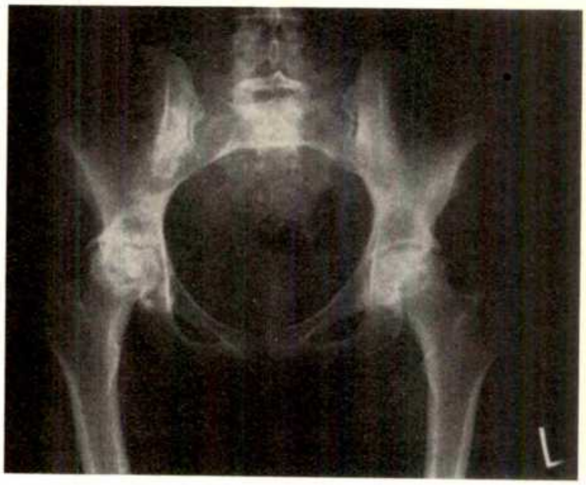

FIG. 5.
Increased changes in femoral heads and acetabulum, 1978.

1979, *British Journal of Radiology*, *52*, 582–584

Hodgkin's disease alone were reported by Timothy *et al.* (1978). The aetiological agents seem to be a combination of chemotherapy and radiotherapy used in the treatment of the disease; prednisone might be the most important drug involved. The time of onset of radiological signs was given by the latter authors as 6 to 21 months before the onset of symptoms.

It is interesting to note that in the single case described in the present report, backache and vague hip pain were constant features of the disease since its presentation, although there were no radiological signs until 12 months after chemotherapy was given, and these symptoms certainly preceded both chemotherapy and radiotherapy. Although the radiological changes as described here would probably fit the diagnosis of osteonecrosis, the pain has always been relieved by radiotherapy.

The problem of management in this particular case is that at the moment the disease appears to be quiescent and for the last three years has shown no sign of activity. The lack of hip movements leads to difficulty with sexual activity, and the orthopaedic surgeons would be willing to carry out a Girdlestone excision arthroplasty to improve the problem. However, if Hodgkin's disease rather than necrosis is the cause of the symptoms, then surgery might light up the disease again. In general, it would appear that one must exclude active Hodgkin's disease in patients with osteonecrosis due to infarction. Failure to do so might lead to dangerous operations, at the same time missing the opportunity to carry out correct treatment.

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Lacrimal, parotid and mediastinal uptake of gallium 67 in sarcoidosis

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The successful use of gallium 67 citrate (^{67}Ga) for the detection of soft tissue tumours was first described by Edwards and Hayes in 1969. Subsequent reports have confirmed its usefulness in the detection of inflammatory and neoplastic processes. Recently we encountered a patient who concentrated ^{67}Ga in the mediastinal nodes and lacrimal and parotid glands. To our knowledge, this triad of findings in sarcoidosis has not been previously described in the literature.

CASE HISTORY

A 48-year-old black woman was referred to the Medical University of South Carolina (MUSC) with a history of continued fever, weight loss and anaemia. She was on no medications other than buffered aspirin for occasional arthritis. The chest X-ray showed mild congestive heart failure and a right hilar mass. Barium enema, UGI, thyroid scan and *in vitro* thyroid function tests were normal. Her haematocrit was 26%. She was transfused with two pints of blood and was treated with penicillin and Keflex.

On admission to MUSC her temperature was 101.5°F. Positive physical findings included enlarged lacrimal and parotid glands, left supraclavicular node, and hepatosplenomegaly. Haematological investigation disclosed a thalassaemia minor variant. Repeat chest X-ray revealed bilateral hilar prominence, cardiomegaly and congestive changes in the lungs. Tomography of the hilar mass was unrewarding. As a diagnosis of lymphoma was entertained, a gallium scan was performed two days after admission. It showed areas of increased uptake in the lacrimal and parotid glands, mediastinal and left supraclavicular lymph nodes. Biopsy of the left supraclavicular node revealed non-caseating granulomas consistent with sarcoidosis.

DISCUSSION

Pulmonary sarcoid lesions are known to accumulate ^{67}Ga (McKusick *et al.*, 1973; Heshiki *et al.*, 1974; Israel *et al.*, 1972; Langhamer *et al.*, 1972; Higashi *et al.*, 1972), but the clinical usefulness of gallium scanning in this disease has not been fully evaluated. Heshiki *et al.* (1974) concluded that while gallium scanning in pulmonary parenchyma or hilar regions correlated poorly with clinical activity, the extent of uptake may prove to be a useful index of disease activity before and after therapy. Israel *et al.* (1972) showed that gallium scanning may prove to be useful in distinguishing enlarged hilar vessels from lymph nodes, but it appeared to have limited applicability in the diagnosis of thoracic sarcoidosis,

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Reprint requests to N. S. Gooneratne.

and further, it was not helpful in the detection of clinically important extrathoracic sarcoidosis.

In the patient described here, uptake of gallium was seen in the parotid and lacrimal glands. Though not specifically described in the literature, moderate uptake in these areas can be seen on reviewing other reported sarcoid cases (Heshiki *et al.*, 1974). In a normal gallium scan, uptake of activity may be seen in the lacrimal and salivary glands, especially in the 24 hour image (Larson *et al.*, 1973). Significant increased bilateral parotid uptake of gallium can be seen due to radiation sialadenitis, post radiation therapy (Bekerman and Hoffer, 1976), and in Sjögren's syndrome (Logic *et al.*, 1976).

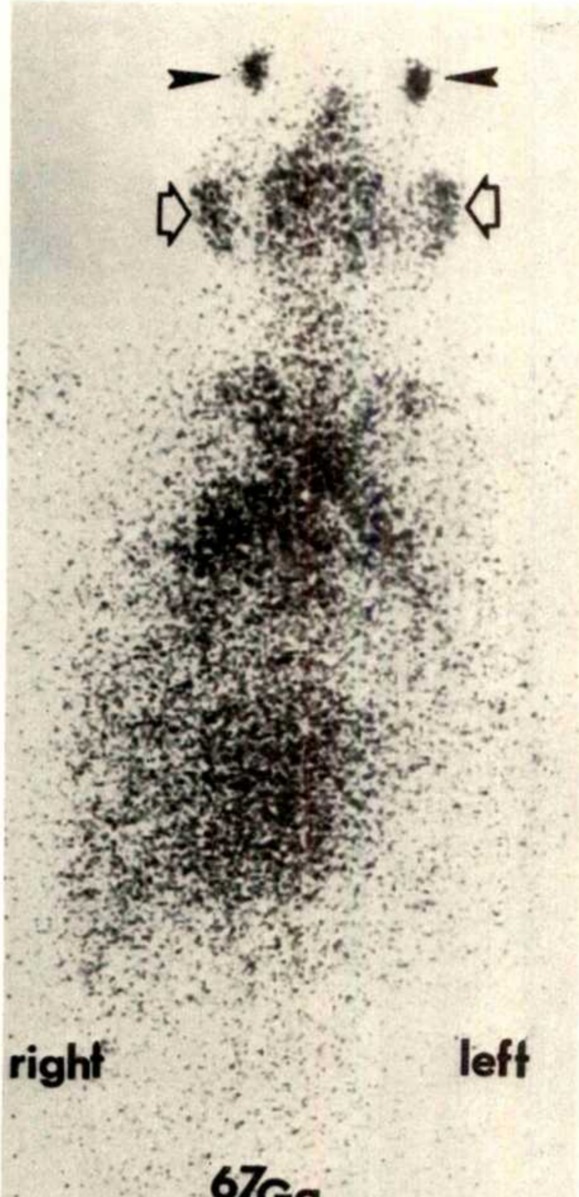

FIG. 1.

Anterior view of 48 hour total body gallium scan showing areas of increased uptake in the chest, lacrimal (arrowhead), and parotid (open arrows) glands.

Lymphoma and sarcoidosis are strong possibilities, especially the latter, in a black patient presenting with a hilar mass, anaemia, weight loss and fever. In 1939, Michelson described uveoparotitis in sarcoidosis with swelling of the lacrimal and parotid glands. Since then this has been a well known entity (Johns, 1972), although the exact incidence of parotid and lacrimal involvement in systemic sarcoidosis is not known. Uptake of gallium in parotid and lacrimal glands, with or without other areas of increased uptake, should prompt the diagnosis of sarcoidosis and lead the clinician to investigate the patient accordingly. We suggest that the observation of the triad, thoracic, lacrimal and parotid uptake of gallium, favours a diagnosis of sarcoidosis rather than lymphoma.

ACKNOWLEDGMENTS

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"Dimple sign" in hepatic vein thrombosis

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The significance of the "hot spot" medial to the gall-bladder fossa on a technetium99m sulphur colloid (^{99}Tc^{m}Sc) liver scan is well documented in the literature (Lee *et al.*, 1976). Among the many different causes of intrahepatic "hot spots" not confined to a specific location are: abscess (Chayes *et al.*, 1974), haemangioma (Volpe and Johnston, 1970), focal nodular hyperplasia, hepatic adenoma (Salvo *et al.*, 1977), and hepatic vein thrombosis (Meindok and Langer, 1976; Staab *et al.*, 1975). In the latter condition, which is often referred to as the Budd-Chiari syndrome, the "hot spot" represents the predominant area of preserved liver tissue. We report the appearance of the liver scan in a case of

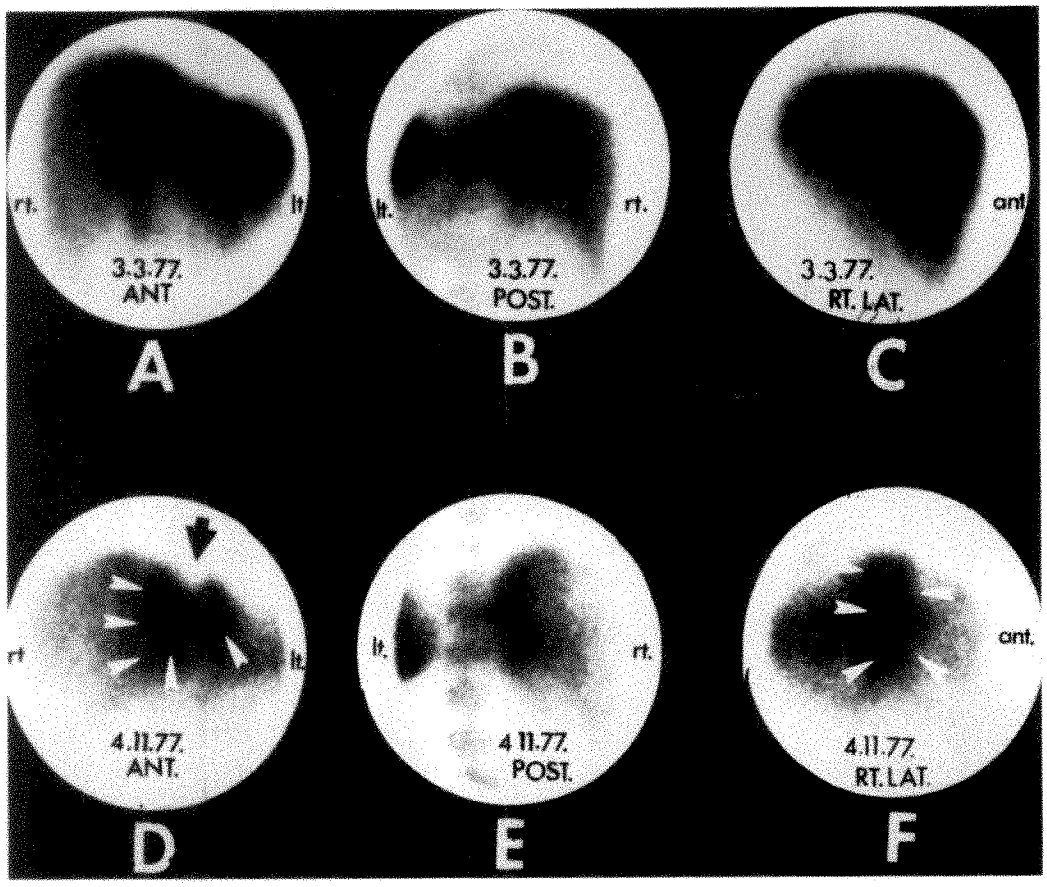

Fig. 1.

A, B, and C: Anterior, posterior and right lateral ^{99}Tc^{m}Sc hepatic scintiscans on 3/77 showing hepatomegaly. D, E, and F: Anterior, posterior, and right lateral views of liver scans of 4/77 showing non-visualization of right and left lobes, "hot spot" (arrow heads), and increased marrow uptake. Arrow in D points to the filling defect ("dimple sign").

hepatic vein thrombosis, including a heretofore unreported finding, which could increase the diagnostic specificity of the liver scan in this syndrome.

CASE HISTORY

A 25-year-old black male was diagnosed in 1974 as having paroxysmal noctural haemoglobinuria, G6PD deficiency and Hb C trait. A ^{99}Tc^{m}Sc liver-spleen scan obtained on a subsequent hospitalization in March, 1977 showed diffuse hepatomegaly (Fig. 1, A, B, and C).

He was hospitalized in April, 1977 with the chief complaint of increasing abdominal girth and intermittent left upper quadrant pain. Physical examination revealed normal vital signs, and a normal chest examination except for a systolic ejection murmur. He had obvious ascites. The liver was enlarged and tender on palpation. He had no peripheral oedema. Initial laboratory investigations included: Hct 20%, WBC 4,000, and platelet count of 50,000. Urinalysis was negative for haemoglobin. A ^{99}Tc^{m}Sc liver-spleen scan (Fig. 1, D, E, and F) was obtained as part of the work-up for ascites in April, 1977. It showed poor uptake by the right and left lobes of the liver, an area of increased uptake ("hot spot") confined to the mid portion of the liver, and increased splenic and bone marrow activity. In the anterior view, a notch-like filling defect was seen at the mid superior border of the liver (Fig. 1D, arrow). The defect was not seen in the right lateral view due to its location.

The initial clinical impression was hepatic vein thrombosis. The ^{99}Tc^{m}Sc liver scan findings supported this diagnosis. The patient was treated with anti-coagulants and later with streptokinase infusion, but his condition deteriorated, and he expired. The autopsy revealed an enlarged liver with centri-lobular congestion and diffuse haemorrhagic necrosis. Also seen were multiple hepatic vein thrombi of varying ages involving tertiary and secondary branches with extension into the larger hepatic veins (Fig. 2).

DISCUSSION

Blood from the left lobe and the central portion of the liver often drains via a composite trunk referred to as the left hepatic vein, into the inferior vena cava. The blood from the right lobe drains via the right hepatic vein into the inferior vena cava. The caudate and quadrate lobe blood drains via the left hepatic vein, and in addition often drains directly into the inferior vena cava. In hepatic vein thrombosis, due to the availability of these additional venous channels, (Meindok and Langer, 1976; Staab *et al.*, 1975), the central portion of the liver often retains its normal functions. The appearance of an apparent "hot spot" in the mid portion of the liver is due to the decreased uptake by the rest of the liver. Additional evidence of hepatocellular dysfunction were increased bone marrow and splenic uptake. The "hot spot" seen in vena caval obstruction is medial to the gall bladder fossa and is on the inferior border in the anterior view, while in the lateral view it is located anteriorly (Gooneratne *et al.*, 1977). In contrast, the "hot spot" in our patient with hepatic vein thrombosis was located superiorly in the anterior view, and in the lateral view it was in the middle third of the liver. While the literature records many reports of hepatic scintigraphic abnormalities in hepatic vein thrombosis, (Meindok and Langer, 1976; Staab *et al.*, 1975) similar patterns have also been observed in constrictive pericarditis, ascites, and post-necrotic cirrhosis (McLaughlin, 1976).

On static liver images, the imprints of the two major hepatic veins show as linear areas of decreased uptake at the superior border of the mid portion of the liver. The filling defect seen at the superior border of the liver ("dimple sign") in our patient could represent an exaggeration of this finding caused by distended, thrombosed hepatic veins, exerting pressure on the adjoining Kupfer cells. A similar imprint at the superior surface of the liver without the "hot spot" has been described due to the cardiac impression (Yeh *et al.*, 1976). In our patient the scan obtained before the onset of hepatic vein thrombosis (3/77) did not show the "dimple sign", and chest radiographs showed no changes in the cardiac contour.

The only definitive diagnostic procedure of hepatic vein thrombosis is contrast venography (Pollard and Nebesar, 1967), which has inherent risks, especially in these gravely ill patients. We suggest that the apparent increased uptake in the central portion of the liver, along with the area of decreased uptake in the mid superior border of the liver ("dimple sign"), may increase the specificity of the ^{99}Tc^{m}Sc liver scan in the diagnosis of hepatic vein thrombosis. As this report concerns only one patient, further work may be needed to firmly establish this finding, but we believe that in the presence of a recent past normal ^{99}TcSc^{m} liver scan, it may be sufficient to arrive at the diagnosis of hepatic vein thrombosis.

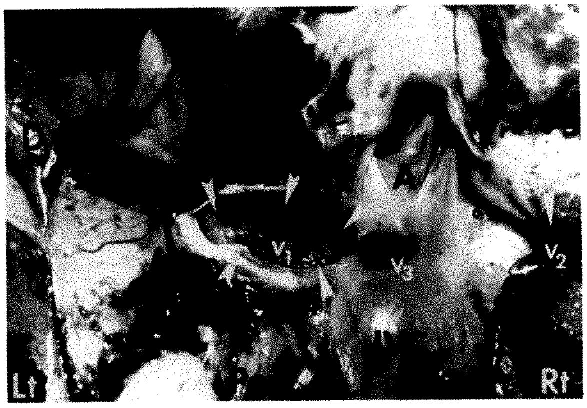

FIG. 2.

Autopsy specimen of liver and right atrium (A) sectioned through inferior vena cava (IVC), and hepatic veins (V_1, V_2, V_3), showing large thrombi (arrow heads) in the left hepatic vein (V_1), and in the right hepatic vein (V_2). D = diaphragm.

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Pulmonary disease caused by the inhalation of cosmetic talcum powder

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The inhalation of talc, a chemical compound of hydrous magnesium silicate, has long been known to cause pulmonary infiltrates (Porro and Levine, 1946; Messite, *et al.*, 1959). As mined, and as used as a lubricant in the leather, rubber and paper industries talc contains considerable impurities including asbestos. Heavy exposure to this industrial grade talc produces radiological changes which include interstitial reticulo-nodular shadowing and pleural plaques (Fraser and Paré, 1970).

Hildick-Smith (1976) in a recent review of the biology of talc points out that domestic talc does not contain impurities, and that people working with this pure talc do not develop pulmonary disease. Work with animals has also failed to show pulmonary disease even after massive exposures to domestic talc (Wagner *et al.*, 1977).

The domestic use of talc might therefore not be expected to constitute a health hazard since not only is the talc used of cosmetic grade, but also the exposure is infrequent and of short duration.

We report a case of chronic pulmonary disease apparently the result of excessive use of domestic talcum powder.

CASE REPORT

A 41-year-old housewife was first seen in March, 1973 when she was complaining of shortness of breath on exercise. A chest radiograph showed a small area of ill-defined shadowing at the right apex. Tuberculosis was suspected but staining and culture of the sputum for tubercle bacilli were repeatedly negative. The Mantoux test was negative at 1 in 10 000 dilution. Exercise tolerance worsened during June and therapy with Rifampicin and Isoniazid was started for a presumptive diagnosis of tuberculosis. Four months later the chest radiograph showed extension of the right apical shadowing and partial collapse with consolidation of the left upper lobe (Fig. 1). Bronchoscopy revealed the left main bronchus to be

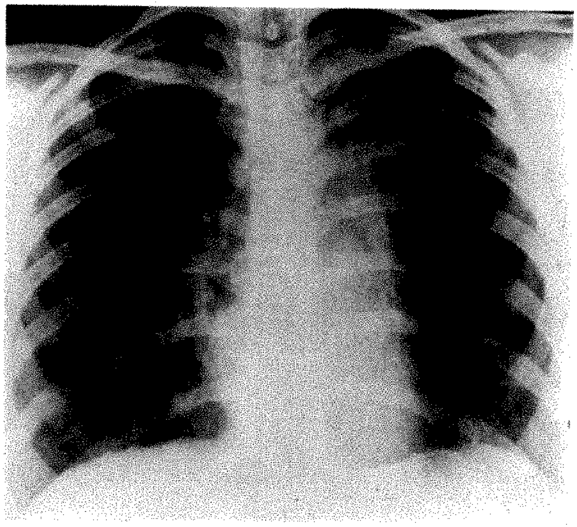

FIG. 1

Chest radiograph showing shadowing at the right apex and collapse of the left upper lobe.

narrowed with inflamed walls. Biopsy of the bronchial wall revealed epithelioid and giant cell systems compatible with sarcoidosis or tuberculosis but no caseation or acid-fast bacilli were present however. Steroids (5 mg Prednisone t.d.s.) were added to the therapy at this time.

After some slight improvement there was again deterioration in exercise tolerance and a dry cough developed in May 1974. The radiograph remained unchanged although respiratory function tests were abnormal (VC 2.15 L, FeV 1.15 L, FeV% 54%). A Kveim test and numerous precipitins including those for aspergillus were negative. Steroid therapy was stopped.

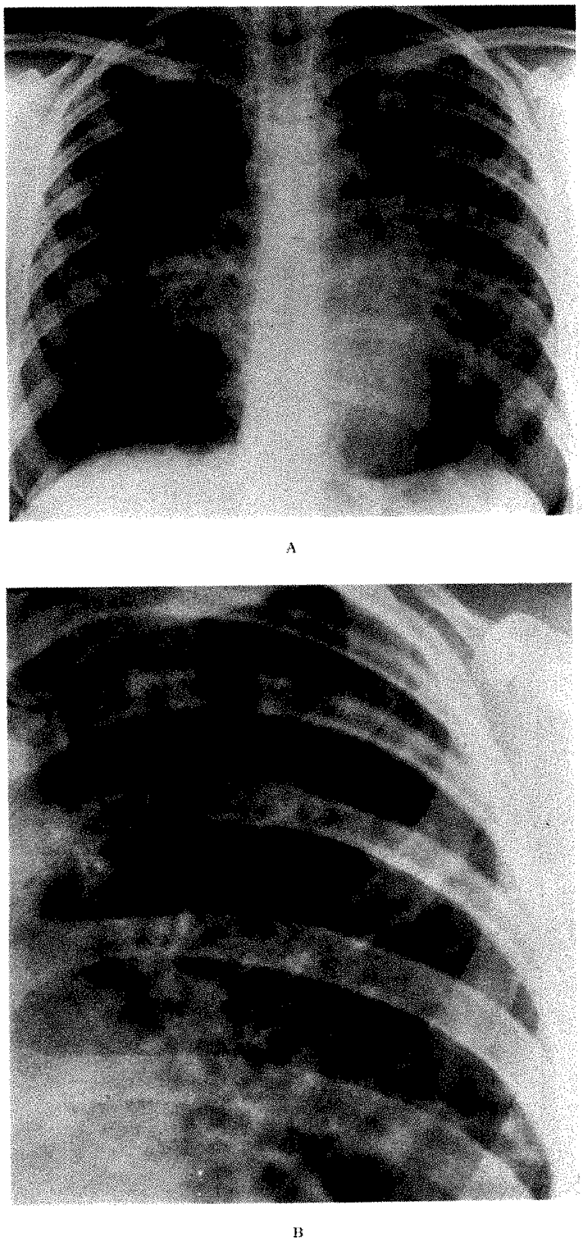

FIG. 2.

(A) Chest radiograph showing widespread ill-defined nodulation. (B) Detail from left upper zone.

In September, 1974 the chest radiograph revealed ill-defined medium sized nodules throughout the lungs with poor definition of the heart borders and hila (Fig. 2A and B). An open lung biopsy was performed.

As a result of the pathology of the lung tissue obtained the anti-tuberculous therapy was stopped. The patient on direct questioning admitted to very heavy use of talcum powder over many years. She was in the habit of dusting the whole body with talc at least once daily. The talc had been applied in a small unventilated room likely to favour inhalation. The talc use was stopped, since when the patient's condition has remained unchanged. She remains short of breath and her chest radiograph has remained virtually unchanged over the last four years.

PATHOLOGY

A piece of firm grey tissue 3 × 2.5 × 1 cm was received. Histologically there were numerous granulomata and extensive fibrosis. The granulomata showed no necrosis, but multinucleate giant cells were plentiful. Staining and culture for acid fast bacilli were negative. With polarized light many birefringent particles were seen, often within the giant cells (Fig. 3). The residual tissue was macerated and the residue inspected by electron microscopy which revealed particles consistent with talc. This was confirmed by the X-ray diffraction pattern.

DISCUSSION

A review of the literature has revealed only three previous reports of pulmonary disease referable to the use of cosmetic talc in adults. Nam and Gracey (1972) report the case of a negro man who had smothered his bed with talc at night for 20 years. He developed pulmonary fibrosis detected at autopsy. Moskowitz (1970) reports a woman who developed dyspnoea and pulmonary reticulo-nodular shadowing after many years as a tester of talc aerosols and Fraser and Paré (1970) report the case of a 31-year-old woman who developed pulmonary symptoms with mediastinal lymphadenopathy, nodular shadowing and areas of consolidation on the radiograph. She had been in the habit of inhaling lavender talc directly from her cupped hands.

Despite the experimental proof to the contrary, it would seem that very rarely cosmetic talc may be implicated in the causation of pulmonary disease. Perhaps an unidentified additional intrinsic factor is necessary before cosmetic talc becomes harmful. Certainly in our case the use of talc has been excessive.

The radiograph may show widespread interstitial nodulation with or without line shadows. There may by lymphadenopathy, and fibrosis has developed in three of the four published cases. The clinical and radiological features therefore are not specific and in particular the differential diagnosis from sarcoid and tuberculosis may be difficult. We would suggest however that a careful history regarding talc usage is taken in patients with resistant pulmonary infiltrates of unknown aetiology. Adequate histological studies

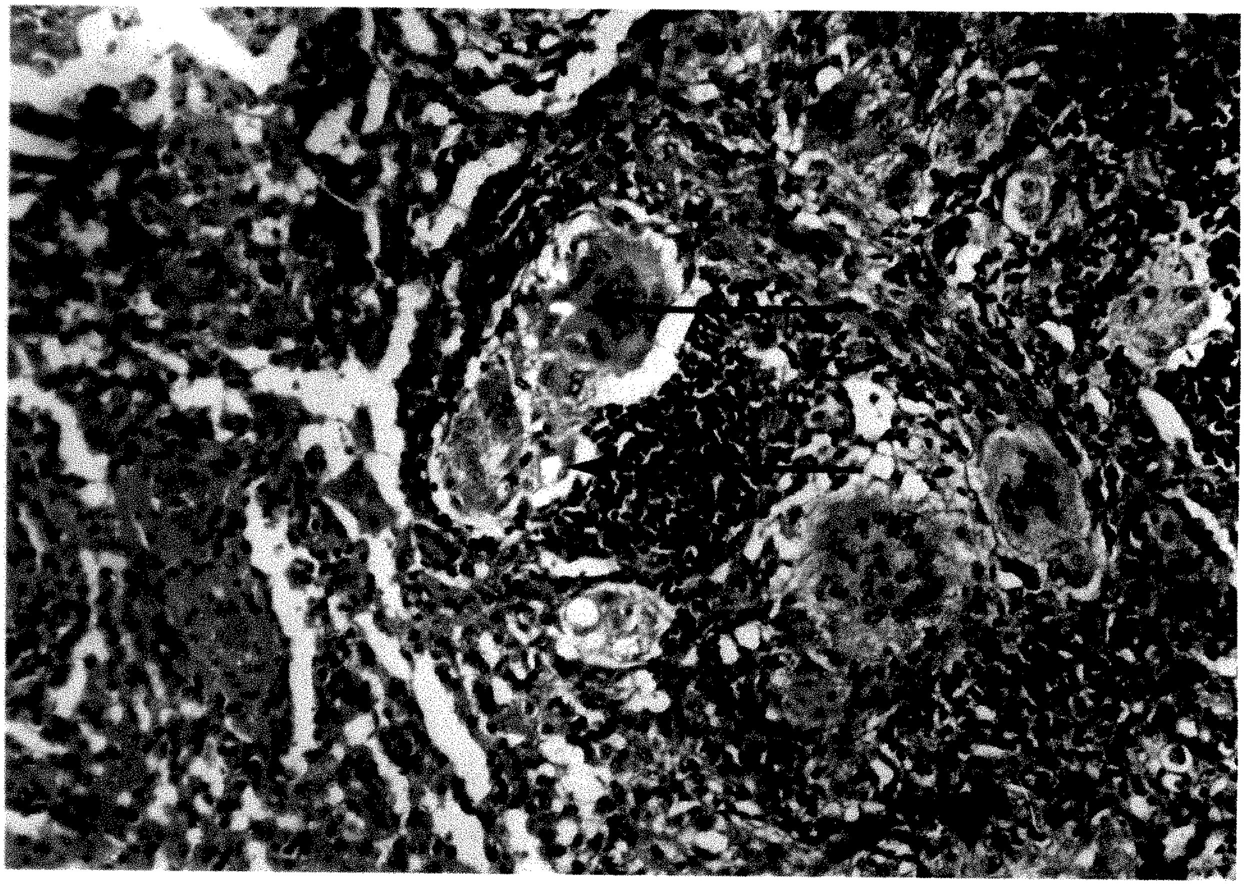

FIG. 3.
Histological section of open lung biopsy showing foreign body giant cells. Some of these contain birefringent crystalline material (arrows). H. & E. ×200. Polarized light.

as outlined in our case are necessary to confirm the diagnosis of domestic talc pneumoconiosis.

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Short communication

On the additivity of hypoxic cell sensitizers in clinical practice

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(*Received October 1978*)

Two questions of concern in the clinical application of hypoxic cell sensitizers are (a) will chemical sensitizers increase damage to normal tissues in a manner similar to hyperbaric oxygen and (b) can sensitizers be combined such that their sensitizing abilities are additive, but their toxicities are not? The first question arises because there is evidence from clinical trials of hyperbaric oxygen of a small, but significant, increase in normal tissue damage relative to air (Dische, 1978). Will the same effect be seen with chemical radiosensitizers? The second question arises because the amount of a sensitizer that can be used, and hence its enhancement of radiation damage, is limited by its toxic side-effects. In the case of misonidazole (Ro 07–0582, Roche Products Ltd.), the dose-limiting side effect is neurotoxicity (Dische *et al.*, 1977). It might be possible to design another sensitizer less toxic than misonidazole such that the two could be combined to give significant sensitization with reduced toxicity. How do the radiosensitizing properties of chemical sensitizers add together?

Adams (1977) has considered the first question. He demonstrated that, because of the shape of the curve relating oxygen enhancement ratio (OER) to oxygen concentration in irradiated cells, the equivalent oxygen concentration to that of a sensitizer giving an enhancement ratio (ER) of (say) two in hypoxic conditions would be quite small. This, when added to the already high concentration of oxygen in venous blood and the tissues being supplied by it, would produce a negligible increase in sensitization. Normal tissues or cells at significantly lower oxygen tensions than venous blood would, however, be expected to be sensitized to radiation. Certain tissues in the body probably do contain cells at much reduced oxygen tensions, *e.g.* cartilage and brain. Consequently one would expect these tissues to be at risk from the use of hyperbaric oxygen or hypoxic cell sensitizers, if they are included in the treatment area.

There is a second reason why sensitizers added to high concentrations of oxygen should produce no additional sensitization. Kinetic studies of the oxygen effect have shown that it can be divided into two components, a "fast" component giving an OER of about 1.7 and a "slow" component responsible for the increase in OER above 1.7 (Shenoy *et al.*, 1975). We have shown that, in the steady state, oxygen and sensitizers giving ERs less than 1.7 (in cultured cells) interact only with damage associated with the "fast" component of the oxygen effect (McNally and de Ronde, 1978). Oxygen at the high concentration found in well oxygenated tissues will act on damage associated with both components, resulting in "saturation" of the "fast" component. Consequently, adding a sensitizer which only acts on this component will not produce any further sensitization. Clinically, the concentration of misonidazole achievable in tissues is unlikely to be sufficient to achieve an ER greater than 1.7 (in fully hypoxic conditions), because of its toxicity. Therefore, there should be no added effect on reasonably well oxygenated tissues.

The additivity or otherwise of sensitizers depends on their respective concentrations which determine whether or not they act on damage associated with the "fast" component of the oxygen effect or that associated with both components. We have already shown that oxygen and misonidazole are only partially additive in V79 cells if they give ERs which are both less than or both greater than about 1.7. If one sensitizer gives an ER greater than 1.7 and the other less than 1.7, then only the larger ER is seen when the two are combined (McNally and de Ronde, 1978). We have now performed similar experiments using V79 cells and combining misonidazole with its principal metabolite, Ro 05–9963 (Roche Products Ltd.), formed by O-demethylation (Flockhart *et al.*, 1978). The methods of growing cells and irradiating them with 250 kV X rays have been described previously (McNally and de Ronde, 1978).

The figure shows results from four separate experiments in which different concentrations of misonidazole and Ro 05–9963 were combined. The lines have been fitted to the data by eye. The enhancement ratios measured from the survival curves are listed in the table. As with oxygen the effect of combining misonidazole with Ro 05–9963 was only partially additive when both drugs were at concentrations giving ERs significantly less than or greater than about 1.7. It follows, therefore, that if the toxicity of any drug limits its use to concentrations giving an ER less than about 1.7, then combining two such drugs can never give an ER greater than 1.7.

In summary, chemical hypoxic cell radiosensitizers will not increase the radiation damage to normal tissues at oxygen tensions similar to that of venous blood. They will, however, sensitize any normal tissues or cells at reduced oxygen tensions and the clinician should be aware of which tissues are at risk in this respect. In practice, adding sensitizers to each other at the low concentrations that are necessary in clinical practice (because of toxicity) may increase the overall enhancement ratio, but not beyond a value of about 1.7. Nevertheless, if the toxic effects are not additive, this could be of clinical benefit.

TABLE I

ENHANCEMENT RATIOS CALCULATED FROM THE SURVIVAL CURVES SHOWN IN FIG. 1. THERE IS PARTIAL ADDITIVITY OF THE EFFECTS OF THE DRUGS ONLY WHEN BOTH VALUES OF ER ARE SIGNIFICANTLY GREATER THAN OR LESS THAN ABOUT 1.7

Misonidazole		Ro 05–9963		Together	Comments
mM	ER	mM	ER	ER	
5	2.20	5	2.40	2.65	Partial additivity
1	1.70	0.1	1.20	1.70	No additivity
0.3	1.30	0.1	1.15	1.46	Partial additivity
0.3	1.30	1	1.60	1.60	No additivity

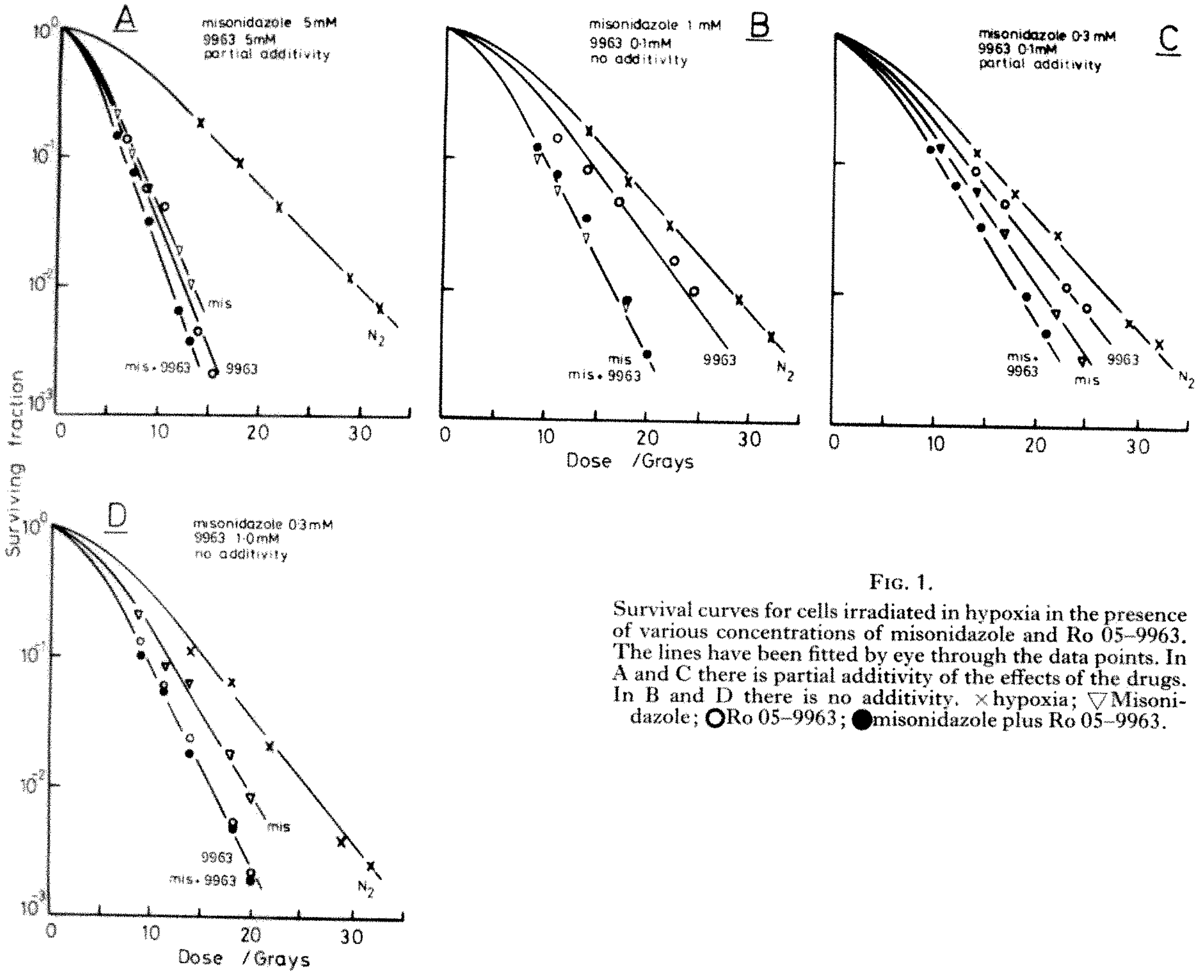

Fig. 1.

Survival curves for cells irradiated in hypoxia in the presence of various concentrations of misonidazole and Ro 05–9963. The lines have been fitted by eye through the data points. In A and C there is partial additivity of the effects of the drugs. In B and D there is no additivity. × hypoxia; ▽ Misonidazole; ○ Ro 05–9963; ● misonidazole plus Ro 05–9963.

Acknowledgment

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

The double contrast meal—new high density barium sulphate powders

THE EDITOR—SIR,

I was interested in Dr. James's experiences (James, 1978) with high density barium preparations for double contrast examinations of the oesophagus, stomach and duodenum. The demonstration of the fine mucosal detail, to show small ulcers and scars, etc., is of course the reason for undertaking double contrast examinations. High density barium preparations give a different coating to standard suspensions, that may make it easier to see the fine mucosal detail. The mucosal layer of barium suspension is considerably more dense radiographically with high density rather than standard suspension. The actual quality of the mucosal layer may also differ. The low viscosity of the high density suspensions may enable the areae gastricae to be seen more frequently. However, from my experience in using both types of suspensions I feel that the higher radiographic density of the large particle suspension makes it easier to see the areae gastricae. These are often present with standard suspensions but not clearly defined. Using low kV ranges (70–85) considerably improves the visualization of the areae gastricae with standard suspensions.

I am rather surprised that Dr. James has achieved successful examinations using high density bariums without the routine use of relaxants. My experience using high density bariums suggests that a completely different double contrast meal technique must be used. With a standard suspension the double contrast meal employs filled and compression views to supplement the double contrast. This is very useful to see various blind areas of the stomach and duodenum, notably the anterior wall of the antrum. Compression studies are not possible with high-density preparations. In the erect the weight of the barium prevents it staying in the cap. It is also impossible to get good compression studies of the antrum. This means that one has to rely solely on the double contrast views. I use relaxants to paralyse the pyloric muscle, so as to obtain optimum views of the cap, loop and antrum. Far from slowing the examination I find that this speeds it up. The commonest cause of delay in barium meal studies is waiting for the cap to fill, and this is overcome by the use of relaxants. Dr. Hunt who has pioneered the high density suspension (Hunt and Anderson, 1976), is also a firm believer in the routine use of relaxants.

The radiologist today has a choice of suspensions for a double contrast examination. The standard suspension can be used to give double contrast, filled and compression views of the stomach and duodenum. Relaxants can be used as necessary. If high density barium preparations are used the examination is entirely double contrast of the oesophagus, stomach and duodenum. Unless special views are taken of the anterior wall there is a danger of missing lesions in this area. I think that the high density preparations are also more technically difficult to use being rather liable to flocculate and provide very poor coating with excess gastric acid. This may be an inherent problem with this type of suspension owing to the lack of suspending agents and the small volume which is employed. However, high density bariums do show advantages in demonstrating the mucosa. Providing the radiologist realizes that there may be limitations in an entirely double contrast study of the stomach and duodenum these types of bariums are worth trying.

Yours, etc.,

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(*Received February 1979*).

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(*In reply*)

The double contrast meal

THE EDITOR—SIR,

In a short communication it is of course not possible to go into detail. My objective was to draw to the attention of radiologists the availability of these new barium preparations and to indicate my opinion that their use markedly improves the demonstration of the areae gastricae. In our practice we find that an areae gastricae pattern is demonstrated almost invariably. The reasons for this better demonstration of the fine detail of the mucosa are at present poorly understood. Work shortly to be published which we have carried out in association with the University of Strathclyde Department of Pharmacy shows some interesting correlations between physico-chemical factors and subjective radiological assessment of the coating properties of different barium suspensions.

To relax or not to relax is a matter of opinion. I would agree that "common sense" might indicate that one ought to be able to achieve a better examination using relaxants. However, I am not aware of any evidence to support this. I have abandoned the routine use of paralysing agents because of the marked increase in time required for completion of the examination. We have measured this to be well in excess of 50%. Dr. Bartram and I must agree to differ on this. It is more difficult to carry out compression studies using high density preparations but it is by no means impossible, especially if one uses small quantities of barium suspension. As far as seeing the anterior wall of the antrum this is in fact possible in most patients using a steep right anterior oblique, right lateral or occasionally right posterior oblique projection in the decubitus position. I am surprised that Dr. Bartram finds waiting for the cap to fill a common delay in barium studies—in our practice we have difficulty preventing the cap from filling before we have examined the stomach. This indeed is one of the main reasons suggested for the routine use of paralysing agents. There are occasional problems with flocculation. This is mainly due to variation in batches and no doubt could be remedied by the manufacturers.

Dr. Bartram and I are evidently agreed on the necessity for carrying out high quality examinations. This was the other objective of my paper—to describe a simple, easily applied and highly accurate technique which usually takes less time to perform than a "conventional" barium meal—whatever that may be!

Yours, etc.,

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(*Received February 1979*).

1979, *British Journal of Radiology*, *52*, 592–593

Correspondence

Radioprotection by vitamin C

THE EDITOR—SIR,

The suggestion by Gregory (1978), that the radioprotective effect observed by O'Connor *et al.* (1977) of vitamin C on hamster ovary cells irradiated *in vitro* is due to scavenging of solvated electrons produced in the cell by the radiolysis of water, raises the interesting problem of how, in general, radiation chemical knowledge can be applied in the radiobiological context.

O'Connor *et al.* (1977) report that cells incubated in a medium containing vitamin C for three days prior to irradiation with X rays are less sensitive to the killing effects of the radiation than control cells. The effect is not large (a dose modifying factor of 1.4 for the highest concentration of vitamin C used; 0.3 mg/ml in the medium) and the evidence for a progressive effect with increasing concentration of vitamin C is weak.

Gregory (1978) suggests that a possible mechanism for this protection involves scavenging of solvated electrons or superoxide anions by vitamin C. This suggestion is based partially upon a hypothesis (Oberley *et al.*, 1976) which proposes that the increased damage resulting when cells are irradiated in the presence of oxygen is due to superoxide anion (O_2) formed by reaction of the solvated electron with molecular oxygen. Alternatively, a more widely accepted hypothesis for the oxygen effect (Alper, 1956) involves the formation of potentially lethal lesions in the cell which, in the absence of oxygen, may be "repaired", but when oxygen is present can react to become "fixed". Support for this latter hypothesis comes principally from two sources, namely the study of the time scale in which reactions to produce enhancement by oxygen take place following irradiation (Michael *et al.*, 1973; Epp *et al.*, 1973) and from studies on the variation of the oxygen enhancement ratio with LET (Alper and Bryant, 1974; Baverstock *et al.*, 1978).

Fundamental to the above arguments is the interesting question of the degree to which foreign materials incorporated into the cell may affect the damage done to the cell indirectly by radicals derived from water molecules interacting with radiation, and even more fundamentally to what extent such indirect effects are responsible for damage. The evidence is contradictory and the arguments too lengthy to discuss here; however, I would suggest that the following conclusions may be reached:

(a) except at very high concentrations direct intervention of added molecules in the reactions of radical products of water with targets in cells seems unlikely because of the very high concentration of cellular materials with which free radicals may react without harming the cell;

(b) indirect action leading to damage of the cells probably takes place close to the site of generation of the radical, and the distinction between direct and indirect action is likely to lie in the nature of the lesion initially formed and not in the extent to which it can be prevented by scavengers;

(c) modification of radiosensitivity by oxygen, for example, probably results from interaction with the lesions once they have formed. The effect on radiosensitivity of radioprotective compounds such as alcohols could be due to a number of causes including modification of energy transfer processes that may result from displacement of water, or from disruption of the normal metabolism of the cell, or from an influence on the repair mechanisms.

Given the above it seems highly unlikely that in the experiments of O'Connor *et al.* (1977) vitamin C acts by radical scavenging to protect cells. In spite of its high rate constants with radicals and solvated electrons its concentration in the cells is small (50 μM at the highest concentration used, assuming 10^8 cells weigh 0.25 g wet).

Two recent papers may, however, give pause for thought. Sverdlov *et al.* (1978) report that the protective efficiency of cysteamine is dependent upon the activity of the repair systems in the bacterium *E. coli*. This sulphur-containing compound had been thought to interact chemically to repair radical damage. Samson and Cairns (1977) reported that *E. coli* exposed to a mutagen, MNNG, over a long period at a low level, became in a matter of hours resistant to its mutagenic effects. To account for this they proposed that by challenging the repair systems a response of more efficient repair can be induced. These two examples illustrate the possible importance of repair pathways. Indeed Alper (1977) draws attention to the possibility of explaining many radiobiological results on a hypothesis of a repair capacity which declines with increasing radiation dose.

In the presence of cupric ions vitamin C has been observed to cause single strand breaks in DNA in solution (Schans, 1978) and in cultured human fibroblasts (Stich *et al.*, 1976). It is interesting to speculate that in the absence of added cupric ion vitamin C might present sufficient of a challenge to the cellular repair systems for the treated cells to be less sensitive to the effects of low LET radiation. This may rationalize the apparent paradox pointed out by O'Connor *et al.* (1977) that the greatest degree of protection is afforded by the vitamin C level most toxic to the cells.

Yours, etc.,
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(*Received December 1978, revised March 1979*)

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Repair and prolonged hypoxia

THE EDITOR—SIR,

Alper (1977) in comparing and contrasting sub-lethal lesion models with repair models of cell survival discussed the effects of oxygenated and hypoxic conditions and the implications of these effects.

Generally, the presence of hypoxic conditions during irradiation (excluding severe anoxia) acts in a dose modifying or dose multiplying manner, in that most of the effect on cell survival curves is equivalent to a change of the dose scale. The influence of this oxygen effect on D_0 can be regarded as an alteration due to the conditions in the number of cellular lesions produced per unit absorbed dose. Normally the extrapolation number of cell survival curves is not affected by the oxygen concentration during irradiation. In these circumstances the number of lesions that cells can withstand before reaching their state of limiting maximal sensitivity on the exponential part of the survival curve can be regarded as unaltered. Some anomalies arising from observations not quite compatible with the above picture of events were discussed by Oliver (1967) who suggested that the period of hypoxia prior to irradiation may be important.

Alper (1977) commented that repair models of cell survival can be used without necessarily including an assumption that the number of lesions per cell that can be repaired or withstood depends on the effects of an agent such as oxygen. However, she also pointed out that observations, after prolonged hypoxia, of changes in extrapolation number inconsistent with purely dose-modifying properties could be understood in terms of repair models in which prolonged hypoxia had an additional effect. This effect would be on the ability of a cell to carry out repair on lesions, or on the amount of a Q-factor. Such observations are not so readily understood in terms of sub-lethal lesion models. She predicted that if prolonged hypoxia had such an additional effect on the amount of a Q-factor, then it might be expected that cells exposed to prolonged hypoxia would demonstrate a lower value of extrapolation number, even if irradiated aerobically, than if they had not been so treated before irradiation.

Results demonstrating that this prediction is correct were published by Foster *et al.* (1971), and earlier by Hall *et al.* (1966). Foster's results showed that the effect of prolonged hypoxia immediately prior to aerobic irradiation reduced the extrapolation number with little or no effect on the slope. Five hours of aerobic culture subsequent to the prolonged hypoxia virtually restored the extrapolation number and shoulder.

Hall *et al.* (1966) showed that prolonged pre-storage in nitrogen reduced the extrapolation number regardless of whether the radiation exposure itself was given in aerated or hypoxic conditions, while the slope reflected the conditions of irradiation. Thus, the extrapolation number is affected by prolonged hypoxia prior to irradiation, irrespective of the conditions of irradiation, and the slope is affected by the conditions of irradiation, irrespective of the previous culture conditions.

The detailed relationship between survival and the time between termination of prolonged hypoxia and aerobic irradiation was studied by Foster *et al.* (1971). Survival increased during the period of the restoration of the shoulder of the radiation survival curve with kinetics similar to Elkind recovery, although the event from which recovery was taking place had nothing to do with irradiation.

Thus at least three effects of oxygen or hypoxia can be identified. The first is the dose modifying effect, the second is the ability of prolonged hypoxia to reduce the extrapolation number, and the third is the ability of oxygen to restore the extrapolation number. The effects can be distinguished in a number of ways other than their different relationship to slope and extrapolation number. For example, they appear to have three different time scales. The dose modifying effect occurs rapidly, the restoration of extrapolation number has a time pattern very similar to that of Elkind recovery, and the reduction in extrapolation number appears from the results of Hall *et al.* (1966) to occur more slowly. The dependence of the effects on the concentration of oxygen may also be different. Neither the concentration of oxygen that produces a reduction in extrapolation number to half nor the minimum oxygen concentration required to promote recovery after oxygen deprivation have yet been determined.

The different natures of the radiation lesions and of the cellular repair processes which act on them can therefore be emphasised. The process demonstrated in Elkind recovery can be distinguished from the repair of actual sub-lethal radiation lesions, and seen more clearly as the recovery of the mechanisms which carry out the repair (Laurie *et al.*, 1972).

Apart from the conceptual importance of distinguishing the different effects of oxygen, the reduction of extrapolation number with prolonged hypoxia could have appreciable clinical implications. If hypoxic cells are sensitized by a reduction in their extrapolation number, then difficulty in curing tumours by low LET radiation can be attributed to the hypoxic cells only if the treatment schedule consists of fractions sufficiently large to offset this sensitisation (Guichard *et al.*, 1977; Habermalz and Fischer, 1976). If the schedule does not achieve this then curability would be governed by the aerated population of cells protected by their possession of a relatively larger extrapolation number.

The above comment on clinical implications is almost exactly that of Berry *et al.* (1970) in concluding their report on findings on radiosensitivity and the oxygen effect for stationary phase cells. It may be suggested that the effects reported above should be considered as simply another manifestation of the properties of cells in the stationary phase. However, this analogy or parallel is unhelpful in that it tends to imply that manipulation of the shoulder for therapeutic advantage should be sought by cell cycle manipulation, whereas other agents that alter the shoulder without reference to the cell cycle may offer better prospects. A more helpful parallel could be with the effects of hypertonic shock, which are comparable to the effects of prolonged hypoxia in the change of shoulder and recovery kinetics (Malone and Foster, 1972; Orr *et al.*, 1975). The time course of hypertonic shock induction of these effects is not really compatible with a description in terms of alterations in the positions of cells within the cell cycle.

Yours, etc.,

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(*Received March 1979*)

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Stimulation of the retina by radium

The Editor—Sir,

In recent issues of this journal there have been three communications concerning the stimulation of the retina by X rays (Cochrane Shanks, 1978; O'Connor, 1979; Emery, 1979), and O'Connor also referred briefly to similar observations with radium. A survey of the radiological literature of the first few years after the discovery of radium in 1898 may therefore be of interest.

The observation that Becquerel-rays, as they were then called, acted on the dark adapted eye was first made by Giesel (1899) when he wrapped a radium preparation in light-proof paper and brought it in the dark near a closed eye. He noted that the sensation of light felt by the eye was strongest when the radium was placed on the eyelid, but was also perceptible when a hand was interposed between radium and the eye or when the radium was placed near the temporal bone. These results were substantiated by several authors including Himstedt and Nagel (1901), while Freund in 1904 described the following experiment conducted by Himstedt (Röntgens' successor in Giessen). "If two perfectly similar little bags of light-proof paper are prepared, the one filled with radium, the other with a corresponding quantity of sand, and if these are placed alternately on the eyes, it is impossible, after about 30 repetitions of the experiment, for anyone to tell on which eye the radium and on which the sand is placed."

It was hoped at one time that this property of radium might help to restore sight to the blind, and studies on blind persons were undertaken by Javal and Curie (1902) at the Blind Institute, Paris, using "a very powerful radium salt" enclosed in a glass tube. They found that the sensation of light perception was only achieved in the partially blind (*e.g.* in a case of retinal displacement) and not in those who were totally blind (*e.g.* in cases of optic nerve atrophy or glaucoma). These findings were confirmed by London (1903) in St. Petersburg—who with Goldberg (Golberg and London, 1903) probably described the first successful radium therapy treatment of cancer, which was reported for two patients with basal cell carcinoma of the face. Wickham and Degrais (1910) also recorded the case history of a patient with glaucoma treated using radium in 1907. The applicator was described as 6 cm in diameter containing 200 mg radium salt, with an activity of 580,000 compared with a standard uranium source. This was the then current unit of activity before the milligram-hour was used. However, the results were unremarkable and the history was described only because it was the first time Wickham and Degrais had used a rubber-covered lead sheet 1·5 mm thick as a filter between source and skin. Previously they had used only cotton wool pads or aluminium sheets. What is of interest, though, is the patient's comment that "during the course of the treatment he seemed to see unaccustomed lights, and felt much encouraged."

The lay press exaggerated the scientific account of these studies with radium on the partially blind; after an article entitled "Hope for the Blind" had appeared in the Neue Freie Presse of Vienna, Kaiser Wilhelm II commissioned an investigation by Greeff (1904) who nevertheless was only able to verify some of the earlier results.

Later, various reports on animal experiments appeared in the literature, the earliest of which were by Birch-Hirschfeld (1904) who applied a 20 mg RaBr capsule to the closed eyes of rabbits for four to six hours, and by Milroy (1905) who irradiated chick embryos from one to three hours, also using 20 RaBr. Information on further investigations of the action of radium (and of X-rays) on the eye has been given by Desjardins (1931).

Yours, etc.,
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(*Received March 1979*)

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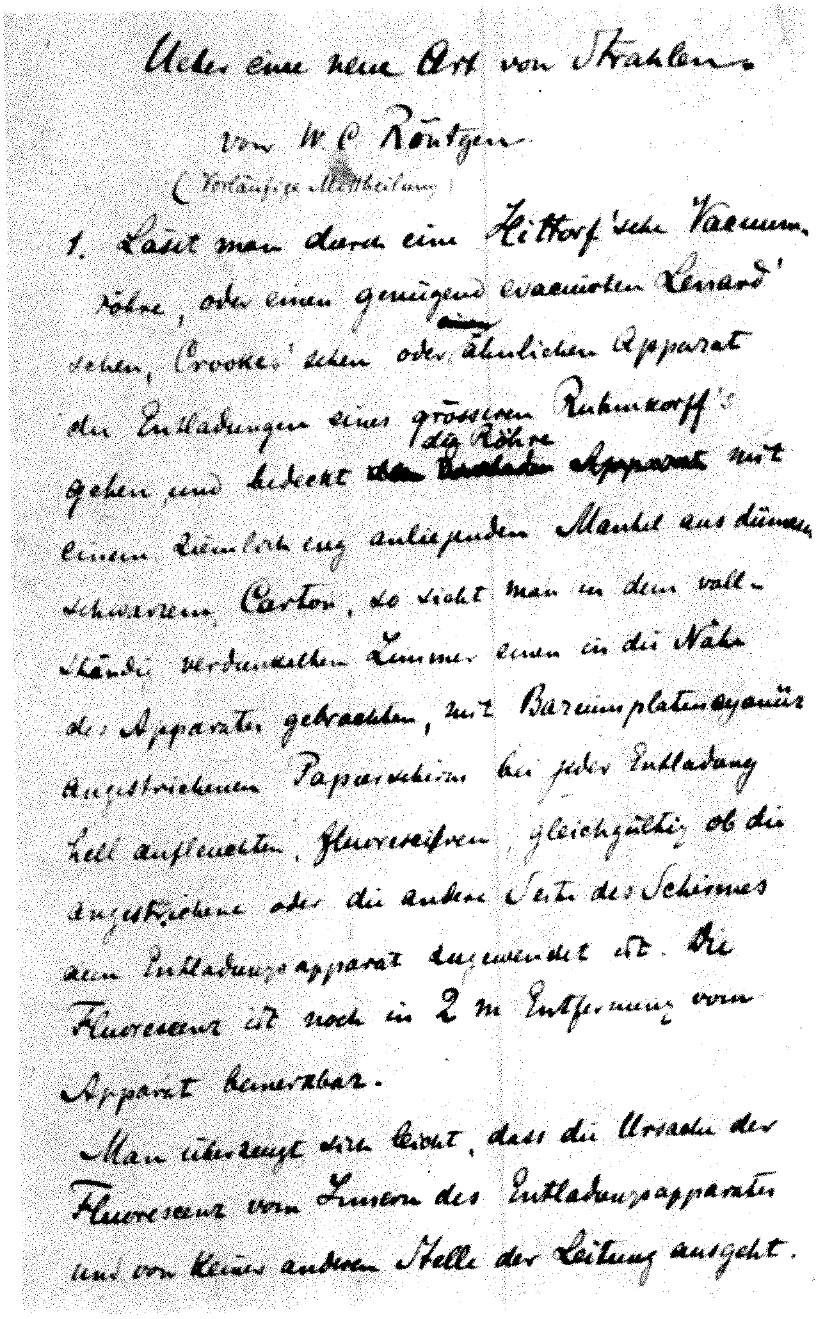
Correspondence

A second "original" first page of Röntgen's manuscript "Ueber eine neue Art von Strahlen"

THE EDITOR—SIR,

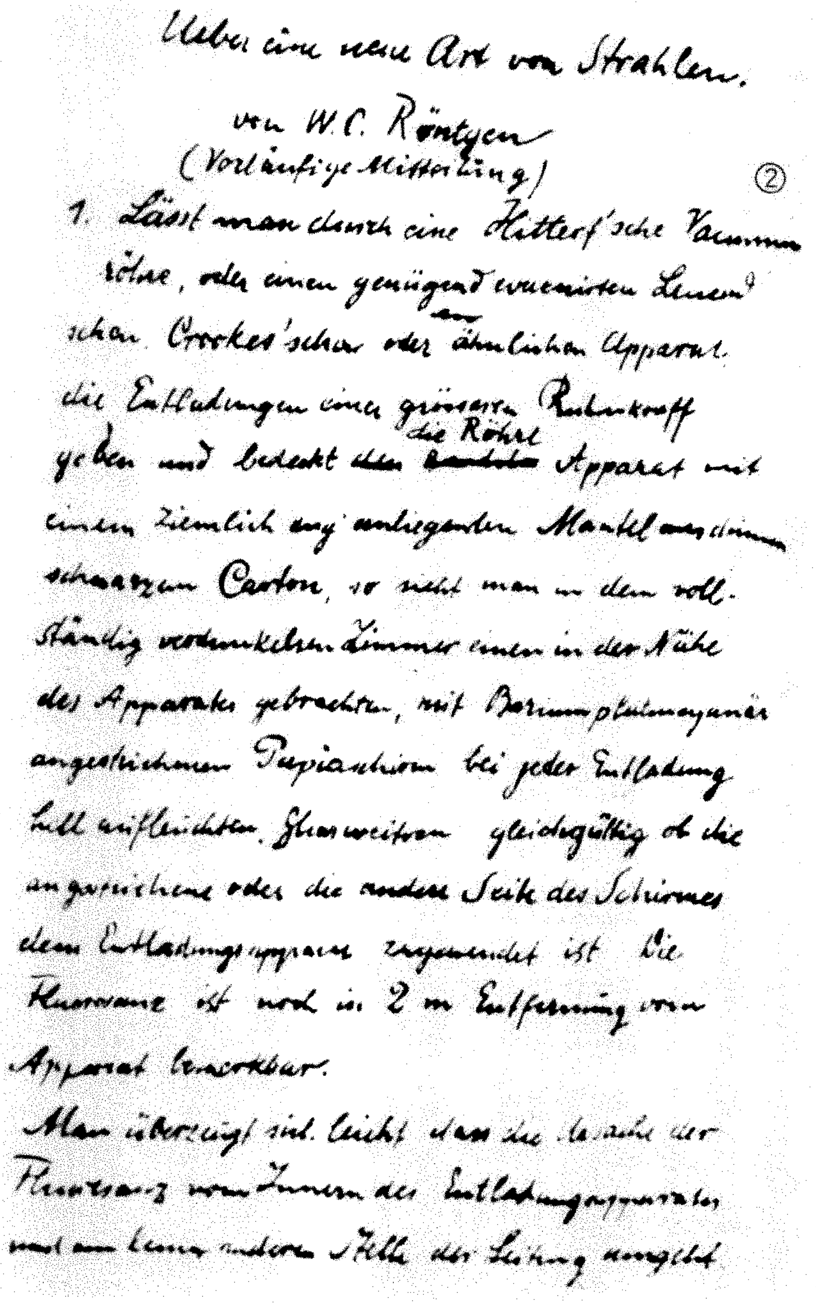
When I visited Würzburg (Germany) in January of this year to look at the collection of "Röntgeniana" exhibited in the Physics Institute of the University, I found to my surprise that the first page of Röntgen's manuscript "Ueber eine neue Art von Strahlen", which is on view there as a facsimile, is not the same as the page studied by Freund (1946) and by me (1978).



Ueber eine neue Art von Strahlen.
von W. C. Röntgen
(Vorläufige Mittheilung)
1. Lässt man durch eine Hittorf'sche Vacuum-
röhre, oder einen genügend evacuirten Lenard'-
schen, Crookes'schen oder ähnlichen Apparat
die Entladungen eines grösseren Ruhmkorff's
gehen und bedeckt die Röhre ~~den [illegible] Apparat~~ mit
einem ziemlich eng anliegenden Mantel aus dünnem,
schwarzem Carton, so sieht man in dem voll-
ständig verdunkelten Zimmer einen in die Nähe
des Apparates gebrachten, mit Bariumplatincyanür
angestrichenen Papierschirm bei jeder Entladung
hell aufleuchten, fluoresciren, gleichgültig ob die
angestrichene oder die andere Seite des Schirmes
dem Entladungsapparat zugewendet ist. Die
Fluorescenz ist noch in 2 m Entfernung vom
Apparat bemerkbar.
Man überzeugt sich leicht, dass die Ursache der
Fluorescenz vom Innern des Entladungsapparates
und von keiner anderen Stelle der Leitung ausgeht.

FIG. 1.

The two hand-written first pages of Röntgen's publication "Ueber eine neue Art von Strahlen". Figure 2, marked by me with an encircled 2, is on view in Würzburg (Courtesy of Physics Institute of the University of Würzburg, West Germany).



Ueber eine neue Art von Strahlen.
von W.C. Röntgen
(Vorläufige Mittheilung)
②
1. Lässt man durch eine Hittorf'sche Vacuum-
röhre, oder einen genügend evacuirten Lenard'
schen Crookes'schen oder ähnlichen Apparat.
die Entladungen eines grösseren Ruhmkorff
die Röhre
geben und bedeckt den ~~[illegible]~~ Apparat mit
einem ziemlich eng anliegenden Mantel aus dünnem
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angestrichenen Papierschirm bei jeder Entladung
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angestrichene oder die andere Seite des Schirmes
dem Entladungsapparat zugewendet ist Die
Fluorescenz ist noch in 2 m Entfernung vom
Apparat bemerkbar.
Man überzeugt sich leicht dass die Ursache der
Fluorescenz vom Innern des Entladungsapparates
und von keiner andern Stelle der Leitung ausgeht.

FIG. 2.

Of course, Röntgen could have written out one or more copies of his manuscript, either to keep for himself or for other reasons. But what is most curious is the fact that both first pages, (Fig. 1) though clearly different on more than 20 points, contain (with one exception) exactly the same corrections. It is not likely that these corrections were made at a later stage and then taken over on the copy, because one of the corrections is the crossing-out of what in all likelihood is a half-finished word. It is the word fragment that I believe I was able to show convincingly in this Journal to be "Entladun" or "Entladu" (1978).

Upon further investigation I came to the following conclusions:

1. I believe the two pages were not written by the same person.

2. On comparison with other texts hand-written by Röntgen (I took for this purpose the reproductions on p. 90 and p. 102 in the second German edition of Glasser's

biography (1959) it is easy to see that the page studied by Freund and myself (on the left in Fig. 1) was written by Röntgen.

3. The way in which the other page appears to have been written (the writer evidently tried to keep the same overall form and to create a superficial likeness) suggests strongly that it is an imitation—for whatever reason.

Dr. W. Petzold of the Physics Institute in Würzburg, who was in fact the first to observe the differences on the occasion of my visit, was as surprised as I was about these findings. At the time he was not sure whether he could trace the source of the copy on display in his Institute.

Yours etc.,
E. FISCHMANN.

Philips Research Laboratories,
Eindhoven, Holland.
(*Received March 1979*)

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New Associate Overseas Editors

After many years of valuable service to *The British Journal of Radiology*, it is with regret that we have to advise our readers that Dr. J. R. Cunningham, our associate editor in Canada, has resigned his position.

However, we have pleasure in announcing that Professor M. Cohen of the Department of Therapeutic Radiology, McGill University, Montreal General Hospital, 1650 Cedar Avenue, Montreal H3G 1A4, Canada, has agreed to take up this vacancy. All papers connected with non-diagnostic radiology originating in USA and Canada should be sent in the first instance for his attention. Dr. P. Armstrong remains our American editor for diagnostic papers.

We would also advise that a new overseas editor, Professor B. J. Cremin of the Department of Radiology, Groote Schuur Hospital, Cape Town, South Africa has been appointed for diagnostic papers and authors in South Africa may send papers for his attention in the first instance.

1979, *British Journal of Radiology*, 52, 598–599

Proceedings of The British Institute of Radiology

The combination of radiotherapy and chemotherapy

Abstracts of papers presented at a British Institute of Radiology meeting held on Saturday, December 2, 1978 in the Reid-Knox Hall, 32 Welbeck Street, London W1M 7PG

Chairman: Professor R. J. Berry

An introduction to the combination of radiotherapy and chemotherapy, by N. M. Bleehen.
Biochemical action of drugs, and possible interactions with radiation, by B. W. Fox.
Evidence for supra-additive tumour cell killing in drug–radiation combinations, by G. G. Steel.
Combinations of cytotoxic drugs and radiation which promote early recovery of mouse bone marrow, by J. L. Millar.
The importance of timing and dose in combined modality treatments, by J. V. Moore.
Promising clinical areas for exploitation of drug–radiation combinations, by M. J. Peckham.

AN INTRODUCTION TO THE COMBINATION OF RADIOTHERAPY AND CHEMOTHERAPY

By N. M. Bleehen

MRC Clinical Oncology and Radiotherapeutics Unit,
The Medical School, Hills Road, Cambridge CB2 2QH

The treatment of cancer depends on control of both the primary disease and potential metastatic spread. The combination of radiotherapy and chemotherapy may therefore have advantages not only because of an increased effect on the primary tumour but also from an adjuvant value on occult or overt metastases. The interaction of the drug and radiation locally may be either additive, more than additive or true sensitization in the situation where the drug itself has no cytotoxicity. The value of these effects in terms of primary tumour control will depend on an enhancement of the therapeutic ratio when a comparison is made with normal tissue effects. The value of the adjunctive chemotherapy on metastases will relate to its efficacy in their control as compared with any increased toxicity to the host or the irradiated tumour volume.

A review of the clinical situation in which such therapy has been used suggests that observed effects of clinical value have related to the added control of metastatic spread. Considerable potentiation of normal tissue reactions in radiation fields has been described with no obvious gain in several studies. The advent of newer sensitizers (outside the scope of this review) may overcome some of these problems, as may a better understanding of the scheduling of cytotoxic regimes and the use of tumour-localizing cytotoxics.

BIOCHEMICAL ACTION OF DRUGS, AND POSSIBLE INTERACTIONS WITH RADIATION

By B. W. Fox

Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX

The prediction of the optimal conditions required for a successful combination therapy by means of a cytotoxic drug and X irradiation must depend on a detailed knowledge of the distribution and half-life of the drug in the whole animal, the biochemical perturbations induced by the drug in the tumour and normal cell populations as well as the mechanism of cell death due to X rays. The pharmacokinetics of certain drugs in humans have been studied in detail, and the use of flow cytofluorography has enabled both short-term and long-term perturbations of a limited number of biochemical parameters to be studied in some detail. However, in order to predict conditions which would provide the highest sensitivity towards X rays, the nature of the cell killing process by X rays must be established. Although the bulk of evidence links a DNA associated damage with chromosomal aberrations and then with cell lethality, the exact causal conditions are not yet recognized. Until these conditions are known in detail, no prediction is possible, in however much detail the biochemical perturbations due to the cytotoxic drug are known. Any synergism between a cytotoxic drug and X rays can still therefore only be determined by empirical choice and timing of agents in humans.

EVIDENCE FOR SUPRA-ADDITIVE TUMOUR CELL KILLING IN DRUG–RADIATION COMBINATIONS

By G. G. Steel

Institute of Cancer Research, Sutton, Surrey SM2 5PX

In the description of the effects of drug–radiation combinations, conceptual and terminological difficulties arise. The most difficult problems are associated with the attempt to examine interaction between two agents whose dose-response curves are non-linear. When dose-response curves are far from linear, as for instance is the case with end-points that involve gross tissue failure, it is probably unwise to attempt to discuss additivity of response. When dose-response curves are not far from linear there is no unique way of calculating the expected additive result but limits can be placed on the possible range of additive responses. When the effects of a combination are considered in terms of iso-effect curves one can describe an envelope of additivity outside which it is possible to regard observed responses as being definitely supra-additive or sub-additive.

In the experimental literature on drug–radiation combinations there is little evidence for interactions that in these terms can be described as supra-additive. A number of drugs, in particular the antitumour antibiotics, interact with radiation and modification of the shoulder of a radiation cell-survival curve is commonly observed. Interaction is often maximal for concurrent administration of drugs and radiation and the effects decline when the time between drugs and radiation is increased. The same is true of normal tissue reactions following combined radiotherapy and chemotherapy and at the present time it is not clear what strategy may lead to the greatest therapeutic advantage from combined treatment.

Reprints of these abstracts may be obtained on application to the Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6867).

COMBINATIONS OF CYTOTOXIC DRUGS AND RADIATION WHICH PROMOTE EARLY RECOVERY OF MOUSE BONE MARROW

By J. L. Millar

Institute of Cancer Research, Sutton, Surrey SM2 5PX

Cytotoxic agents such as cytosine arabinoside, chlorambucil and methotrexate reduce radiation-induced lethality when given two days before the irradiation. It can be shown that improved survival results from a more rapid recovery of the haemopoietic stem cells (CFU–S) in animals that receive the pretreatment compared with animals that received the radiation alone. This earlier stem-cell recovery eventually promotes a more rapid peripheral blood recovery in these pretreated animals.

In the recovery pattern of the CFU–S in mice given 9 Gy irradiation alone, there is a lag phase of three to four days (with the possibility of a post-treated dip) before recovery begins. Pretreatment with cytotoxic agents such as cytosine arabinoside remove this lag phase and recovery begins promptly after the irradiation. It has been shown that non-cytotoxic compounds, such as the purine nucleosides given immediately before the irradiation, will also promote early recovery of the CFU–S. It is unclear if this observation is related to the enhanced recovery promoted by cytoxic agents.

To exert its full effect a purine nucleoside such as guanosine must be given before irradiation and not after. This suggests that a cell population is being protected by guanosine administration although it has been established that guanosine administration does not alter the radiosensitivity of CFU–S. It is possible that there is a cell population more primitive than the CFU–S whose radiosensitivity is reduced by treatment with a cytotoxic agent two days before, or a purine nucleoside immediately before, irradiation. It would be from this population that the CFU–S is rapidly replenished so manifesting an early recovery.

THE IMPORTANCE OF TIMING AND DOSE IN COMBINED MODALITY TREATMENTS

By J. V. Moore

Paterson Laboratories
Christie Hospital and Holt Radium Institute,
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In cancer treatment, the adjuvant use of cytoxic drugs with radiation carries the risk of increased injury to involved normal tissues. The probability of an observable change in response can vary both with the dose of the agent(s) and the interval between their administration. To a greater extent than for radiation, the sensitivities (1/slope) of stem cells in different tissues to graded given doses of drug can be expected to vary: *e.g.* D_{37} for cyclophosphamide-treated marrow $CFU_s \approx 100$ mg kg^{-1}; for jejunal crypt clonogenic cells ≈ 550 mg kg^{-1}. As regards timing, the experimental literature reveals that the adjuvant use of many commonly-used cytotoxic drugs can result in either an increase in, or "protection" from, radiation injury (*e.g.* vincristine, arabinosyl-cytosine, hydroxyurea in gut; actinomycin D, hydroxyurea in skin). These changes in response with the same adjuvant agent occur over only a few hours and the time-response relationship varies markedly for different drugs. That the level of radiation injury may be altered when a drug is given days before or after must also be considered, particularly for adriamycin (demonstrated experimentally for skin and lung). It is concluded that experimental studies of adjuvant treatment should include a full time course of response, preferably in more than one tissue.

PROMISING CLINICAL AREAS FOR EXPLOITATION OF DRUG–RADIATION COMBINATIONS

By M. J. Peckham

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Drugs and radiation are widely employed in clinical practice with several objectives.

1. Situations in which cytotoxic drugs are employed to treat systemic disease, and radiation employed to treat either a primary tumour mass (as for example Ewing's sarcoma and rhabdomyosarcoma) or a "sanctuary" site, for example the central nervous system in acute lymphoblastic leukaemia. Where there appears to be a good prospect of control of small-volume metastatic disease with chemotherapy, but where recurrence tends to occur in bulky tumour, radiation is also employed to treat sites of initial bulky disease, for example in oat cell carcinoma of the lung and Hodgkin's disease. In these clinical situations the effectiveness of the combination will obviously depend upon the ability of chemotherapy to eradicate metastases outside the radiation field.
2. Drugs and radiation may be employed to increase the probability of local control of tumour with irradiation. In this situation chemotherapy is being employed to modify the radiation response and may be used concurrently, before or after irradiation.

While there is clear evidence of the efficacy of combined chemo/radiotherapy in the first category, particularly in the paediatric tumours, evidence for improved radiation control in patients receiving chemotherapy and radiotherapy is scanty. Experimental studies using the Lewis lung carcinoma have demonstrated that volume reduction with cyclophosphamide can modify the radiation dose-response curve (Stanley *et al.*, 1977). In most clinical situations where drugs have been used in close temporal proximity to irradiation, enhanced radiation tissue damage has been observed. It is proposed that the most promising line of clinical exploitation of combined chemotherapy and radiotherapy is to adopt a sequential approach in which chemotherapy is employed initially to achieve tumour volume reduction. A recent clinical study reported by Nervi *et al.* (1978) offers some support for the view that tumour volume regression can increase the probability of local radiation control.

Studies are in hand investigating the timing of drugs and radiation in relation to normal tissue damage, the recovery of normal tissues following exposure to cytotoxic drugs and tumour re-oxygenation following chemotherapy.

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1979, *British Journal of Radiology*, 52, 600–602

Radiation chemists talk to biologists

Abstracts of papers presented at the Radiobiology Work-in-Progress meeting held on January 19, 1979 at the Reid-Knox Hall, 32 Welbeck Street, London W1M 7PG.

Chairman: E. M. Fielden

Chemical and biophysical concepts applied to radiobiological processes, by G. E. Adams.
Free-energy relationships with radiosensitizers, by P. Wardman.
Free radical cascades and the interaction of radiosensitizers and radioprotectors, by K. D. Asmus, D. Bahnemann, H. Basaga, J. Dunlop, J. S. Mahood, J. E. Packer, A. J. Searle, T. F. Slater, R. L. Willson and B. Wolfenden.
On the mechanisms of radiosensitization by nitrous oxide, by N. Vrantzas and A. Tallentire.
Direct/indirect effect: an irrelevant concept in cellular radiobiology?, by K. F. Baverstock.
Bacteriophage. The link between radiation chemistry and radiation biology, by D. L. Dewey.
Molecular mechanisms of phototherapy, by R. V. Bensasson, C. Salet, R. W. Sloper, T. G. Truscott and E. J. Land.
Laser flash photolysis and fluorescence studies of the interaction of the excited states of furocoumarins with DNA in solution, by P. C. Beaumont, B. J. Parsons, S. Navaratnam, G. O. Phillips and J. C. Allen.

CHEMICAL AND BIOPHYSICAL CONCEPTS APPLIED TO RADIOBIOLOGY PROCESSES

By G. E. Adams

Physics Division, Institute of Cancer Research, Sutton, Surrey

In the temporal classification of radiation processes generally it is convenient, although somewhat arbitrary, to define the onset of the radiation chemical stage as the dielectric response time of the irradiated medium. In water this is of the order of 10^{-12}sec. Various versatile fast response methods permit the quantitative measurement of many radiation chemical processes occuring in the nano-, micro- and millisecond timescale. In addition, fast response techniques capable of measuring rapid radiation processes at the cellular level are also now available, although the time resolution is usually 10^{-4}sec or longer. Some applications of these techniques are used to illustrate the role of radiation chemical processes in mammalian cell systems.

In particular, the oxygen effect, which is almost universal throughout radiobiology, is free radical in origin. It is known that there is more than one mechanism of the oxygen effect. Oxygen is not unique in its sensitizing ability; it is but one member of a large class of chemical substances which are able to act as hypoxic cell sensitizers. The sensitizing abilities of all these compounds correlate directly with their electron affinities and this relationship affords considerable insight into the mechanisms of cellular radiation damage and its modification. With few exceptions, the efficiencies of these compounds, expressed in terms of the concentrations required for sensitization, show little variation with cell type or absolute cellular radiation sensitivity. Some of the properties of oxygen-like sensitizers are used to discuss the relative importance of direct and indirect action in the initial stages of cellular radiation damage.

Short-lived luminescence is induced in solid DNA irradiated with single 3-nanosecond electron pulses. Oxygen, or small amounts of chemical sensitizers present in the DNA matrix, cause quenching of part of the luminescence. The results provide strong evidence that energy can migrate considerable distances in DNA and that some sensitizers—oxygen included—can function as long-range electron traps. The relevance of these results to intracellular radiation chemical processes is discussed.

FREE-ENERGY RELATIONSHIPS WITH RADIOSENSITIZERS

By P. Wardman

Cancer Research Campaign, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN

This paper outlined the importance and application of measurements of changes in Gibbs free energy (ΔG) and related concepts. The interrelationships between ΔG, rate and equilibrium constants, differences in electrochemical reduction potentials and Hammett σ substituent constants were described. The mathematical methods used to analyse changes in biological responses to chemicals with changes in free-energy related parameters were outlined and examples given of free-energy relationships with radiosensitizers. Postulated mechanistic schemes (even for quite complex reaction sequences) can yield predictions of the dependence of a biological response or rate of a model chemical system upon free energy. One example was discussed (reaction of a reduced flavin with nitro compounds).

FREE RADICAL CASCADES AND THE INTERACTION OF RADIOSENSITIZERS AND RADIOPROTECTORS

By K. D. Asmus,* D. Bahnemann,* H. Basaga, J. Dunlop, J. S. Mahood, J. E. Packer, A. J. Searle, T. F. Slater, R. L. Willson and B. Wolfenden

Brunel University, Uxbridge UB8 3PH;
*Hahn-Meitner Institute, Berlin, Germany**

The interaction of natural and exogenous sensitizing and protecting chemicals has often been used to account for the varying extents of cellular damage occuring under different irradiation conditions: the effects of metronidazole and dithiothreitol on bacteria or bean roots is an example (Asquith *et al.*, 1974).

Sensitizers are often (not always) electrophilic in nature while protectors are generally nucleophilic, *i.e.* good electron donors. Interaction can occur directly, *e.g.* N-ethyl maleimide + sulphydryl compounds; nitroxyl free radicals + ascorbic acid or glutathione; oxygen or organic nitro compounds + ascorbic acid or sulphydryl compounds in the presence of ferrous ions.

Sensitizers and protectors may also compete for oxidized free-radical lesions. This may result in oxidation and

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consequent fixation, or reduction and possible repair, *e.g.* oxygen, nitroxyl or nitro compounds may compete with ascorbate or sulphydryl compounds (Redpath and Willson, 1973).

Competitive interference with the reactions of radical-cations and radical-anions may also occur. Pulse radiolysis studies show that these species formed by indirect action as well as by direct ionization react with other molecules and can enter into sequential electron transfer cascades. The extent of repair of potentially lethal radical-cation lesions (for example on guanine residues) by electron donation from radical-anions or other molecules such as cysteamine, vitamin E or ascorbic acid, can thus be affected (Willson *et al.*, 1974).

In some cases such reactions may lead to the formation of toxic products. The effectiveness of electrophilic compounds such as metronidazole as radiosensitizers may thereby be increased. The effectiveness of nucleophiles as radioprotectors, however, may be reduced; indeed with iodide or chlopromazine the toxic effect can predominate and they can act incongruously as radiosensitizers (Shenoy *et al.*, 1975).

Interestingly, the radical-cation of chlorpromazine, the likely toxic species, can be quenched by vitamin E or vitamin C (ascorbic acid), alone or by sequential electron transfer, thus suggesting a protective "cocktail" for reducing the toxic side effects of this and related drugs.

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DIRECT/INDIRECT EFFECT: AN IRRELEVANT CONCEPT IN CELLULAR RADIOBIOLOGY?

By K. F. Baverstock

MRC Radiobiology Unit, Harwell, Didcot, Oxon OX11 0RD

Over the past several decades the radiation chemistry of water has been investigated using dilute aqueous solutions of molecules which will react with the free radicals produced by the absorption of ionizing radiation by water molecules. Energy is thus directly absorbed by water molecules at the site of energy deposition and indirectly transferred to solute molecules by the inherent reactivity of free radicals which diffuse from their sites of formation to become more or less homogeneously distributed in the solution.

Radiobiological experiments have been reported on yeasts, mammalian cells and bacteria to determine to what extent cells are damaged by reactive free radicals. Organic compounds which react rapidly with free radicals have been added to cells during irradiation and the degree of protection they afford measured. The high concentrations of additives required to achieve any reduction in sensitivity indicates that the target (most probably DNA) is well protected and that free radicals need to be produced within 3 nm of the target if they are to be effective. A consequence of this is that damage sites in the DNA are likely to be closely related spatially to the sites of energy deposition both when the energy is directly deposited in the DNA and when it is indirectly transferred to DNA by free radicals. Thus the more or less uniform distribution of damage events implied by indirect action will not necessarily be observed in cellular systems even at low LET. This has particular implications for experiments in which attempts are made to correlate DNA strand damage with cellular endpoints such as survival over a range of radiation qualities since techniques of strand break analysis are based upon the assumption that the distribution of breaks is random. Since the average size of energy deposition events from the passage of an ionized particle is several times greater than is required to break a chemical bond, the possibility that more than one damage site will result from the passage of an ionized particle close to the target may be significant at low LET and will become increasingly likely at higher LET values.

ON THE MECHANISM OF RADIOSENSITIZATION BY NITROUS OXIDE

By N. Vrantzas and A. Tallentire

Manchester University, Manchester M13 9PL

Spores of *Bacillus pumilus* E601 have been irradiated with gamma rays in water suspensions equilibrated with N_2O in the presence of the OH scavenging agents KSCN, t-butanol or ethanol. Determinations were made of H_2O_2 formed in the spore suspensions together with measurements of radiation sensitivity. At sufficiently high concentrations these scavengers remove N_2O sensitization, indicating involvement of the OH radical in the process of sensitization. Accumulation of H_2O_2 occurs in suspensions with scavengers present and, provided that scavenger concentrations are high enough, build up of H_2O_2 occurs over the dose range where spores are exhibiting a low sensitivity. At low initial scavenger concentrations, exhaustion of scavengers occurs at relatively low doses, and further increase in dose causes a dramatic decrease in the level of H_2O_2 with concomitant increase in spore sensitivity. It is suggested that loss of H_2O_2 results from its reaction with OH radicals to give HO_2 radicals. Oxygen formed from the dismutation of two HO_2 radicals may well account for sensitization seen when N_2O is present in suspension.

BACTERIOPHAGE. THE LINK BETWEEN RADIATION CHEMISTRY AND RADIATION BIOLOGY

By D. L. Dewey

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When bacteriophage are purified and irradiated in dilute aqueous suspension, they are inactivated by indirect effects resulting from the deposition of the primary energy in water to yield radicals which obey the laws of radiation chemistry. Oxygen and other radical scavengers protect against biological damage by radiation.

When bacteriophage are irradiated in concentrated nutrient broth containing biological concentrations of thiol-containing molecules, they are very much more resistant to radiation. Oxygen is now a sensitizer in the manner well known to radiobiologists.

The mechanism of inactivation is also completely different in dilute suspension and in broth. In the former, the radicals formed by radiation absorbed in water react with a trigger mechanism located in the phage tail, causing the premature release of the phage DNA. In the latter case, the inactivation is due to the direct absorption of energy in the DNA, causing double strand breaks and base damage.

By taking the phage apart, irradiating the component parts and then reassembling these parts to reform complete, live phage, it can be shown how the direct and indirect actions of radiation can be measured separately and the contribution of each determined under different experimental conditions.

MOLECULAR MECHANISMS OF PHOTOTHERAPY

By R. V. Bensasson and C. Salet

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R. W. Sloper and T. G. Truscott

Department of Chemistry, Paisley College, Paisley PA1 2BE

E. J. Land

Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester, M20 9BX

Light irradiation of jaundiced infants is widely used for reducing bilirubin concentrations in the blood and tissue, being easier to carry out than the previous therapeutic technique of blood replacement transfusion. The action spectrum of photodestruction of serum bilirubin suggests that the therapy operates via light absorbed directly by bilirubin. It has been proposed that phototherapy causes self-sensitized photo-oxidation of bilirubin, the oxidation products being formed via $^1O_2$ generated by energy transfer from triplet excited bilirubin. Pulse radiolysis and laser flash photolysis have been employed to determine several properties of triplet excited bilirubin. The low singlet→triplet crossover-efficiency found does not support self-sensitized photo-oxidation via the triplet, but rather a mechanism involving recently detected unstable polar photoisomers of bilirubin formed via the singlet excited state.

The newly introduced photochemotherapy (PUVA) treatment of psoriasis involves application of psoralen followed by near UV light irradiation. Psoralens intercalate between the base pairs in duplex DNA, and the therapeutic effects are believed to be mediated by the photochemical formation of crosslinks. Both theoretical and experimental evidence supports the involvement of triplet excited psoralen in forming such crosslinks. Pulse radiolysis and laser flash photolysis have been used to measure psoralen singlet→triplet crossover, and to follow reactions of psoralen triplets with nucleic acid bases and amino acids *in vitro*. Efficient quenching reactions were observed, but only a small percentage was found to lead to a duct formation. Energetic considerations excluded the possibility of photochemotherapeutic side-effects occuring via psoralen to thymine triplet energy transfer.

LASER FLASH PHOTOLYSIS AND FLUORESCENCE STUDIES OF THE INTERACTION OF THE EXCITED STATES OF FUROCOUMARINS WITH DNA IN SOLUTION

By P. C. Beaumont, B. J. Parsons, S. Navaratnam, G. O. Phillips and J. C. Allen

School of Natural Sciences, The North E. Wales Institute, Kelsterton College, Connah's Quay, Clwyd CH5 4BR

The triplet states of 8-methoxypsoralen (8-MOP) and 4, 5′, 8-trimethyl-psoralen (TMP) have been generated using laser flash photolysis techniques and their reactivities with DNA constituents investigated. No reaction could, however, be detected with any base, nucleoside or nucleotide (limits of approximately 10^6 dm^3 mol^{-1} s^{-1} or less). These data contrast sharply with results from similar experiments with psoralen where rate constants of up to 400 times greater were obtained (Bensasson *et al.*, 1978).

In the presence of DNA (0·3% w/v) itself, the yield of psoralen triplets was found to be reduced to 20% of the yield obtained in the absence of DNA (25 ns after the laser flash). In contrast, no such decrease was found for 8-MOP. In the case of both 8-MOP and psoralen, the lifetimes of the observed triplet states increased with increase in DNA concentration.

DNA was also found to have an effect on the fluorescence emission from psoralen and 8-MOP. In both cases, substantial decreases in the total fluorescence yield were observed together with shifts of the emission maxima to shorter wavelengths. These fluorescence results can be taken to indicate the extent of binding of the furocoumarin to DNA.

A possible explanation of the above data is that the yield of triplet states from bound psoralen molecules is virtually zero while the yield of bound 8-MOP triplets is considerably greater (∼0·14). Even if bound psoralen triplet states are very short-lived (<25 ns), it is difficult to reconcile the triplet precurser model for skin photosensitization (Song *et al.*, 1971) with the similar skin-sensitizing efficiencies of these drugs.

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Erratum

It has been brought to our attention that the telephone number for Dr. Jeffrey J. Lesser in the Letter to the Editor on "The plight of radiologists in Russia", *British Journal of Radiology, 52,* 164, should have appeared as 01–636 7170.

We apologize for any inconvenience this error may have caused.

Forthcoming events and other notices

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of penultimate month preceding publication (*i.e.* April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Association of Radiation Oncologists of India

This newly formed scientific association specializing in radiation therapy has been established to promote the scientific development of the speciality and practice of radiotherapy in India. Any enquiries regarding this newly formed association should be addressed to the Honorary General Secretary, Association of Radiation Oncologists of India, Department of Radiotherapy, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

IV European Congress of Radiology

The IV European Congress of Radiology will take place in Hamburg (German Federal Republic), September 4–8, 1979.

Scientific programme:

diagnostic research of organs of the upper abdomen;
diagnostic research in nuclear medicine: organs of the upper abdomen;
radiotherapy in tumours of the genital system of males and females;
radiobiology and X-ray protection (combined therapies and risks of ray exposure);
radiophysics and techniques (methodical problems in diagnostics and in planning of radiotherapy).

Enquiries: Secretary of the IV European Congress of Radiology, Postfach 10 64 07, D-2000 Hamburg 1, Federal German Republic.

Quantitation of Tumour Response: a Critical Appraisal

The L.H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to stimulate a critical appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

Nuclear Medicine in Urology

A combined meeting of the British Nuclear Medicine Society and the North West of England Urological Club will be held at Manchester Royal Infirmary on October 19, 1979.

It is intended to hold a morning session of invited papers and discussion of techniques and recent developments, followed by an afternoon session on clinical applications. There will be an opportunity to visit the Departments of Nuclear Medicine and Medical Physics, and the meeting will end with a dinner.

For further information, please contact Dr. H. J. Testa, Consultant in Nuclear Medicine, Manchester Royal Infirmary, Manchester M13 9WL.

Paediatric Radiology

A two-day course in diagnostic paediatric imaging will be held at the Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London WC1 on November 15–16, 1979. The main theme of this course will be the respiratory/cardiovascular system.

Further details and application forms are available from The Secretary, Department of Paediatric Radiology, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

The British Medical Ultrasound Society
11th Annual Scientific Meeting

To be held on December 17–18, 1979 in Edinburgh.

Authors wishing to submit contributions for consideration should send the title and 100–200 word abstract to the address below before September 15, 1979. Additional background information on the work would help in planning the programme.

Address for enquiries: Dr. W. N. McDicken, Department of Medical Physics and Medical Engineering, The Royal Infirmary, Edinburgh EH3 9YW.

5th International Congress of the International Radiation Protection Association

Will take place in Jerusalem, Israel, March 9–14, 1980.

The scientific programme of the Congress will cover all aspects of radiation protection with emphasis on its central theme: radiation protection—a systematic approach to safety.

An interesting programme has been planned including a commercial exhibition and pre- or post-congress workshops and Professional tours.

Social events and a programme for accompanying persons have been organized.

For further information: The Secretariat, 5th International Congress of IRPA., PO Box 16271, Tel Aviv, Israel.

Symposium on Spine and its Contents

EAR "Symposium Vertebrologicum" (Spine and its Contents) will be held from April 23–25, 1980 in Prague, Czechoslovakia.

The subjects of this symposium will be recent advances and experiences in:

(a) Equipments and investigative methods of spine and spinal cord.
(b) Radioanatomy and physiology of spine and spinal cord.
(c) Radiodiagnosis of pathological conditions.
(d) Interventive (diapeutic) radiodiagnostic methods.

For further information contact The secretariat of "Vertebro 1980", PO Box 88, Sokolská 31, 120 26 Praha 2, Czechoslovakia.

Forthcoming events

XV INTERNATIONAL CONGRESS OF RADIOLOGY

The XV International Congress of Radiology will take place June 24–July 1, 1981 in Brussels, Belgium.

The scientific activities of the Congress as well as the scientific and technical exhibitions will take place in the Brussels Exhibition Centre.

Further information from: Secretariat ICR-81, Ave. Winston Churchill 234B-Box 16, B-1180 Brussels, Belgium.

Obituaries

Sir Peter Kerley, K.C.V.O., M.D., F.R.C.P., F.R.C.R.

We regret to announce the death on March 15, 1979 of Sir Peter Kerley, Consulting Radiologist to the Westminster Hospital.

Peter James Kerley was born on October 27, 1900 at Dundalk in Ireland. He studied medicine at University College, Dublin, where he qualified in 1923 and obtained the M.D. in 1932. Meanwhile he had studied in Vienna, and took the D.M.R.E. in 1925. From then on he made an outstanding success of his chosen speciality and, without doubt, became one of the most eminent radiologists in the world. He brought great intellectual qualities to his work and to these he added a diagnostic flair which constantly astonished his colleagues. In a period when radiology was perhaps less of an exact science than it has become since, this gift was of enormous importance and helped to establish the true importance of the subject. His period as Consultant at the Westminster Hospital saw the rise of thoracic surgery as a major sub-speciality and P. K. (as he was universally known) became one of the world's leading cardio-thoracic radiologists. The experience was reinforced by his association with the National Heart Hospital.

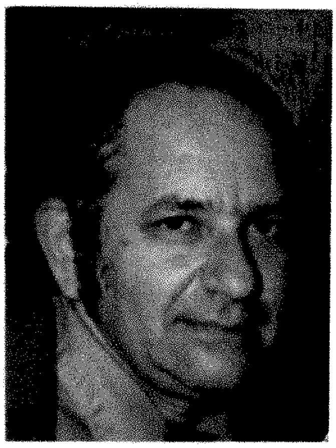
Sir Peter Kerley's influence was also felt as adviser to the Ministry of Health (as it then was) on radiology and by his association with many radiological bodies; amongst other tasks he was editor of the *Journal of the Faculty of Radiologists*, now *Clinical Radiology*, for some years, and he was President of the Faculty of Radiologists from 1952–55. When, in due course, the Faculty became the Royal College of Radiologists, he was awarded its gold medal in 1976. He was honoured by numerous radiological bodies abroad; thus he was an honorary fellow of the American College of Radiology and of the Radiological Society of Chicago; of the Australasian College of Radiology; the Faculty of Radiologists of Ireland and the Radiological Society of Toronto.

Dr. Kerley was responsible for making the diagnosis of the bronchial neoplasm which later was to claim the life of King George VI. He was made a C.B.E. in 1951 and created a C.V.O. in 1952. The elevation to a knighthood in 1972 gave him great pleasure. But his most lasting memorial will be his work and writings. "Kerley's lines" have become so well known that they are now used by every medical student, and many other observations he made have been so deeply incorporated into the corpus of radiological knowledge that it is now difficult to identify their progenitor. In 1938, with Dr. Cochran Shanks, he edited the first edition of *British Authors*, a textbook of radiology which has remained a cornerstone of radiological teaching in its various later editions ever since.

P. K. brought a great zest to living. With him passes one of the most illustrious members of the profession.

F. STARER

Victor Berman, M.B. (Cape Town), D.M.R. (London)



Dr. Victor Berman who died on January 18, 1979 was born and educated in South Africa. He qualified in Cape Town in 1941 and served as a Captain in the Medical Corps of the South African Army. At the end of the war he came to London for postgraduate study in radiology, mainly at the Westminster Hospital where he was much influenced by the work of Sir Peter Kerley. He returned to South Africa to consultant appointments in Johannesburg in hospitals both for black and white patients: he was also Director of Radiology at the Childrens Hospital. His fluency in Afrikaans was a great asset in his work.

Among his publications were papers on childhood duodenal ulcers and on hyperplasia of Brunner's glands of the duodenum.

In 1963 he and his wife Reeve decided to return to London and he was immediately appointed Consultant Radiologist to a group of hospitals in East London, St Leonard's, Metropolitan, Bethnal Green and the London Jewish. (At the last mentioned his fluency in another language, Yiddish, also proved an asset). His sudden death at the early age of 60 was a profound shock and sorrow to his colleagues and his many friends. He leaves a widow and two sons, one a dental surgeon and the other a doctor.

I. KELSEY FRY

E.P. writes I first met Victor when we were students on the D.M.R. course. His warm nature, his kindness and his generosity were immediately and strikingly evident, and his genial sense of humour unquenched even by the rigours of life in post war London. His love, and his knowledge of music were intense and every moment of leisure was spent at concerts. With a characteristic chuckle he commented that he propped up the Albert Hall.

After their return to London he and his wife established a large circle of devoted friends and kept open house for visitors. All who knew Victor loved him, and his premature death has caused great sadness and a deep sense of loss.

Book reviews

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A user's guide to diagnostic ultrasound 579

Books received

Receipt of the following publications is acknowledged as a courtesy to the sender. These publications have been lodged in the library of the British Institute of Radiology for the use of members.

Prevention and Detection of Cancer. Part II – Detection. Vol. I: High Risk Markers. Detection Methods and Management. Edited by H. E. Nieburgs. 1978, pp xxi + 1328 (Maurice Dekker, Inc. New York), Sw. fr. 190.
ISBN 0–8247–6683–0.
IEC Publication 613: *Electrical, Thermal and Loading Characteristics of Rotating Anode X-ray Tubes for Medical Diagnosis*, 1978. pp 33, (Commission Electrotechnique Internationale, Geneva),Sw. fr. 39.

Controlled Therepautic Trials in Cancer Edited by R. Flamant and C. Fohanno (UICC Technical Report Series, vol.32), 1978, pp. xxix + 684, Sw. fr.28.
ISBN 92–9018–032–3.

International Agency for Research on Cancer – Annual Report 1978, pp. 185, (World Health Organization), £4·20.
ISBN 92 832 1078 6.

Epidurography. A diagnostic aid in spinal lesions. By R. C. Gupta, 1978, pp.83.

Computers in the Control of Treatments Units

The British Institute of Radiology: Special Report No 16, March 1979

by R. E. Bentley, A. L. Bradshaw, C. A. F. Joslin, W. J. Redmond, M. E. Rosenbloom, B. J. Scholl-Evans, J. B. H. Stedeford and R. C. Tudway.

Digital computers are being used very successfully in radiotherapy dose computation. This report deals with another, at present less highly developed, application of computers, the provision of some degree of automation at the point of treatment. Drawing on their own practical experience, on information from manufacturers and on the relatively sparse literature on this topic, the authors analyse the reasons for wishing to introduce some automation, discuss suitable techniques and procedures and make specific recommendations. Practical problems in implementing such control systems, including the need to gain acceptance from those operating the equipment and from those being treated, are carefully considered.

The authors were of a multidisciplinary Task Group, convened by Dr. Roy Bentley, which had been set up by the British Institute of Radiology Working Party on "Applications of Modern Technology in Radiotherapy."

The report should be of interest to all those concerned as users, designers or manufacturers with future developments of radiotherapy apparatus.

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The British Journal of Radiology

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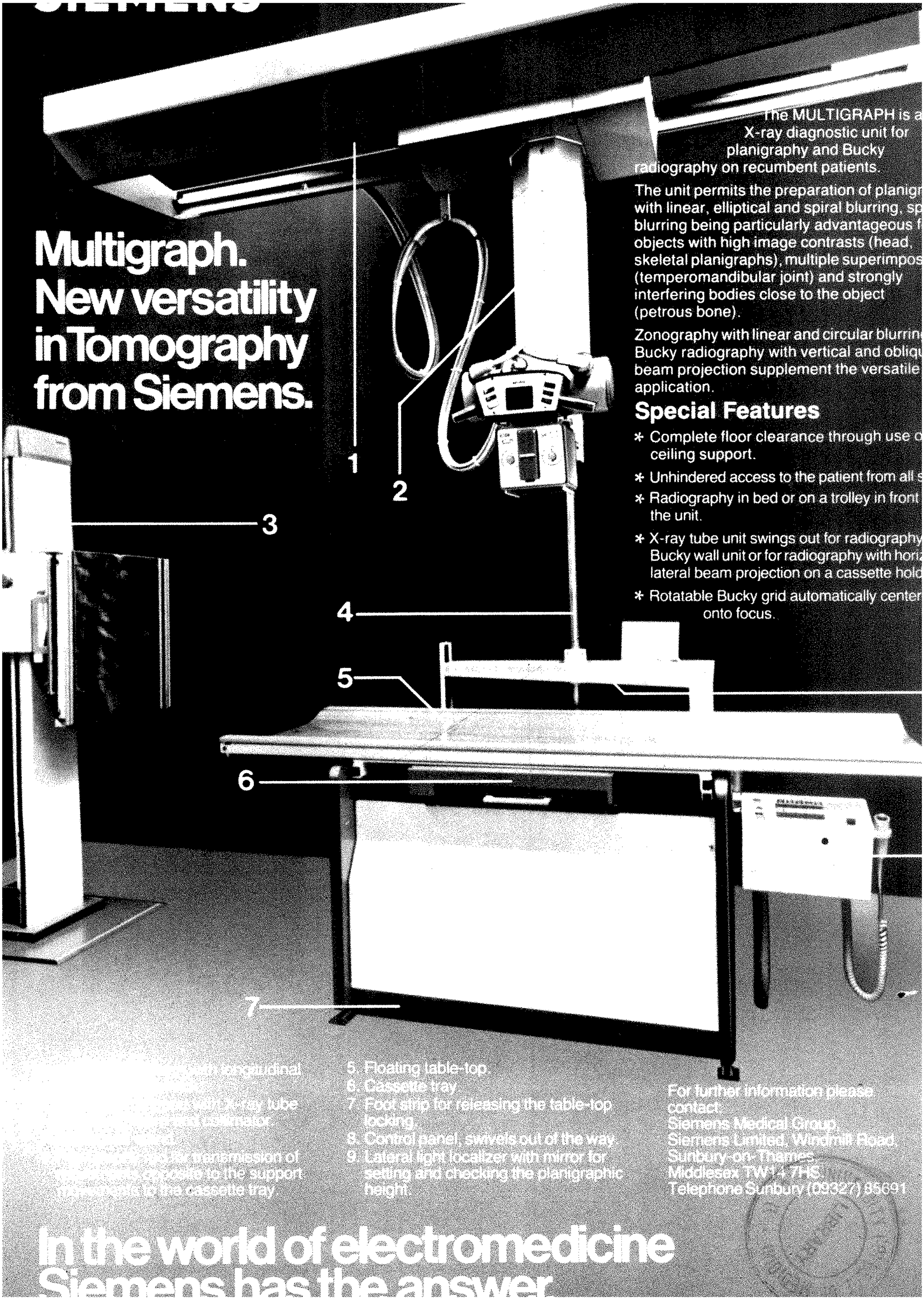

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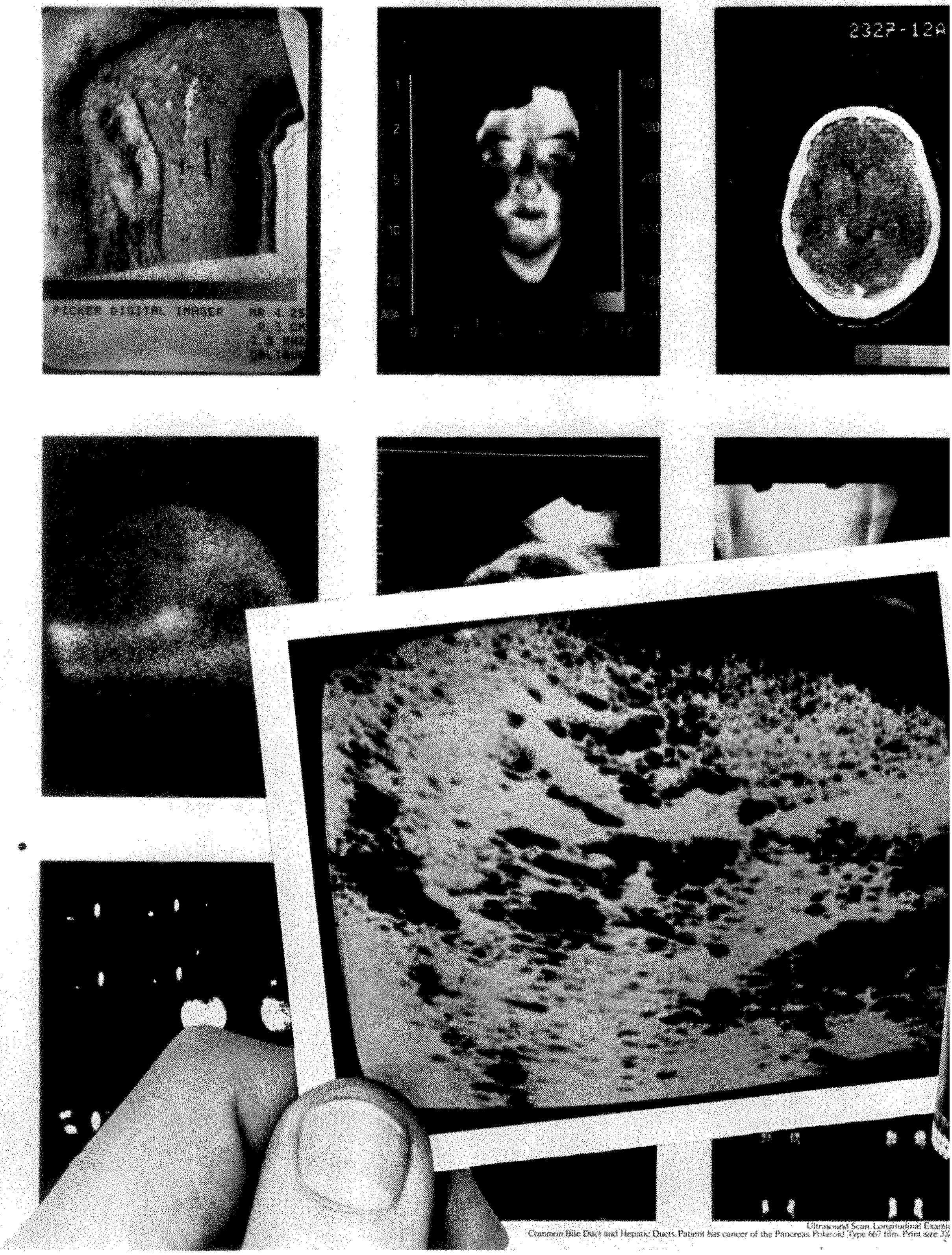

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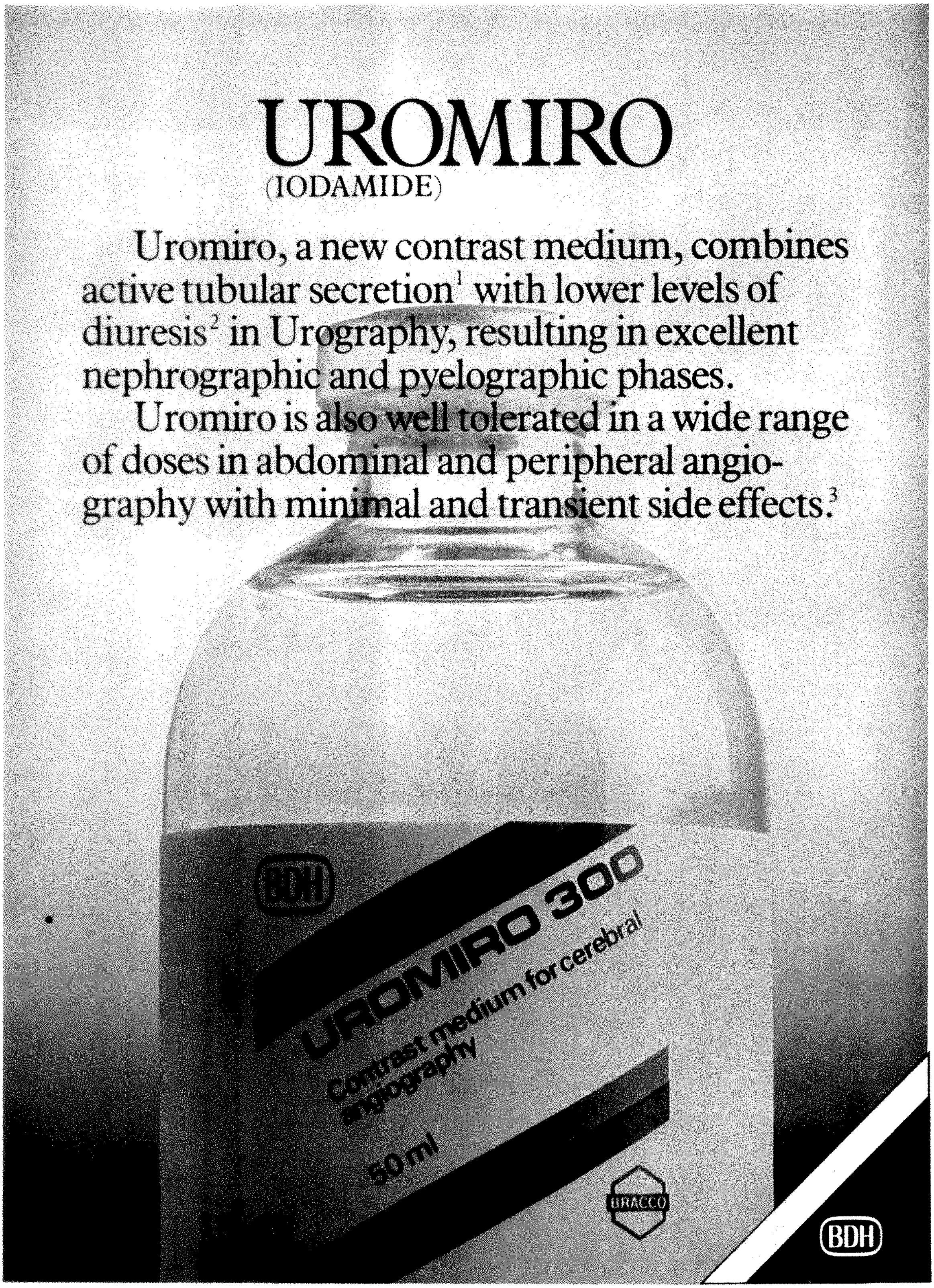

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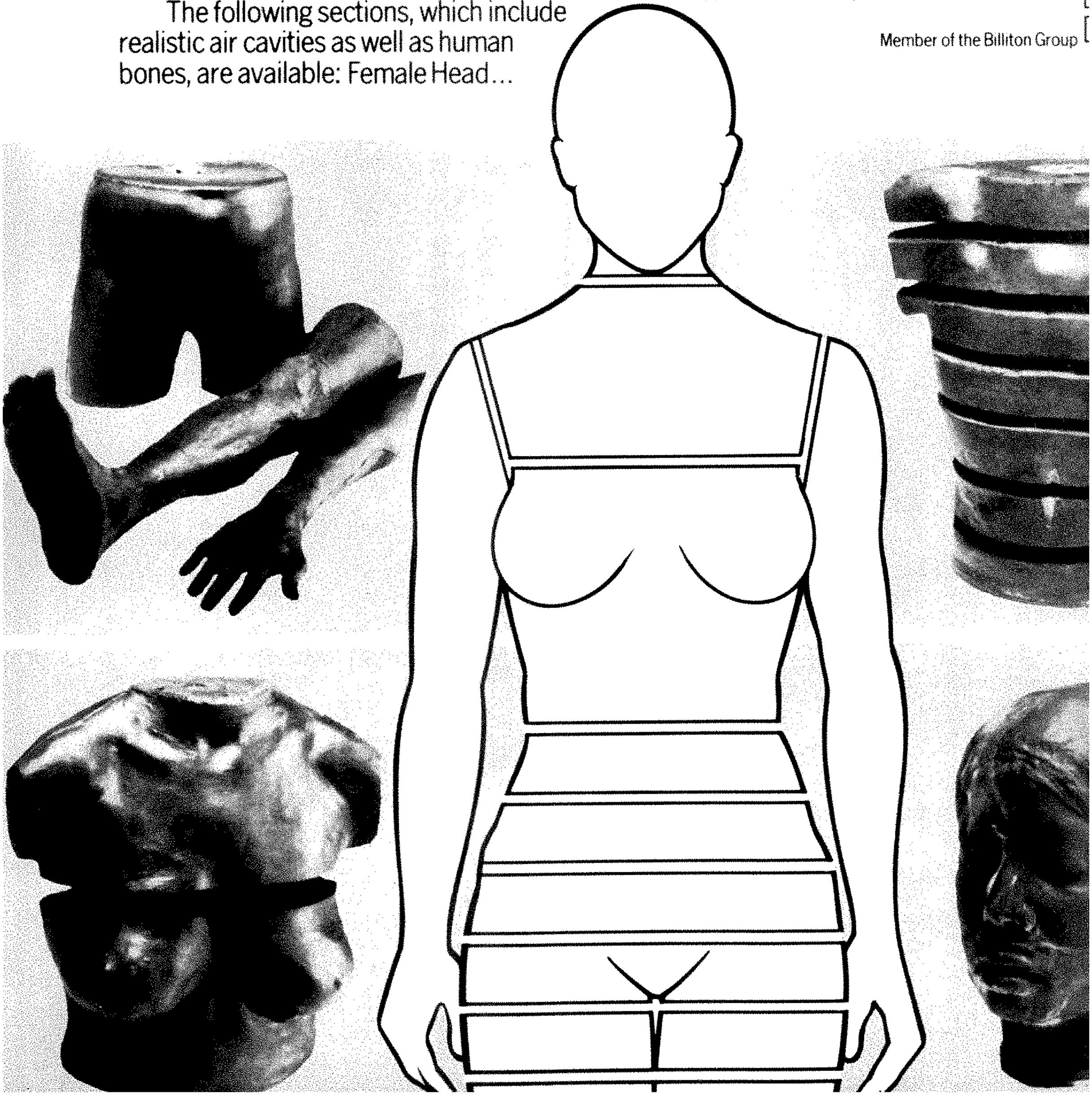

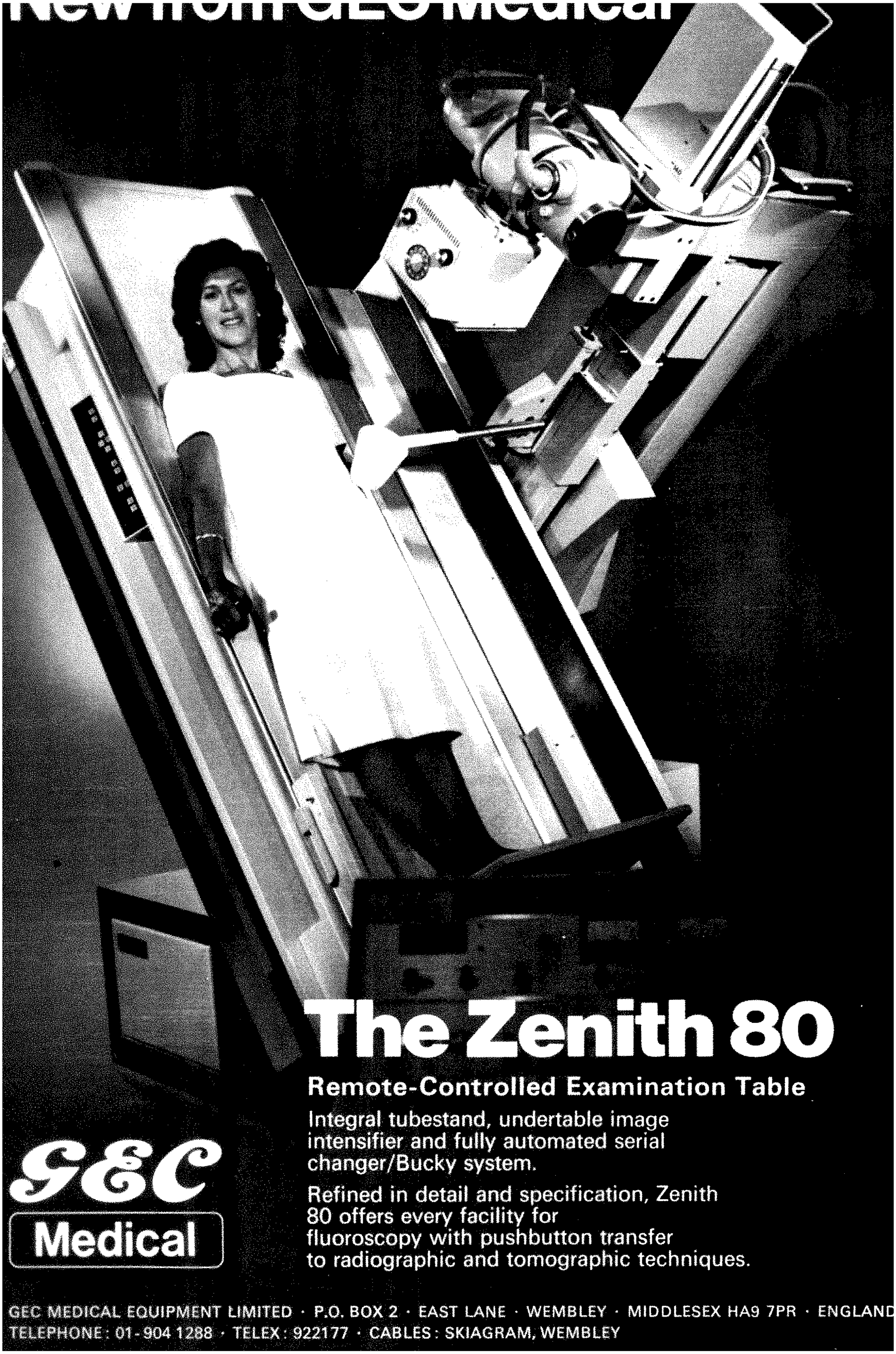

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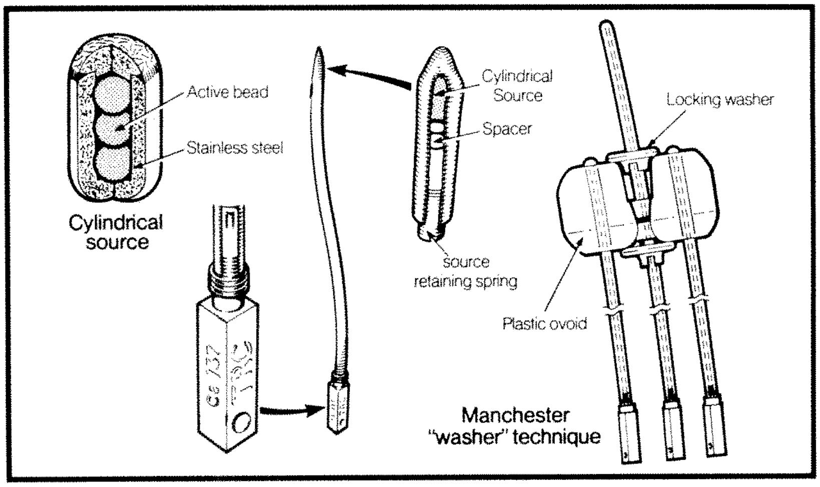

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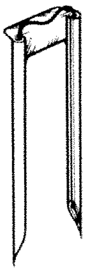

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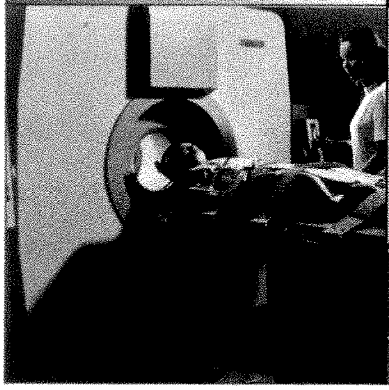

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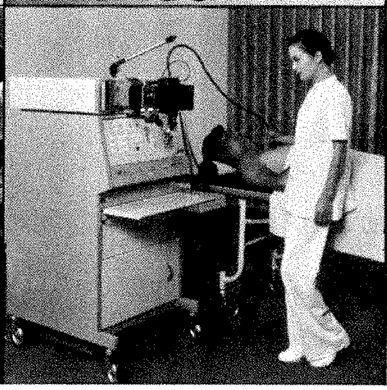

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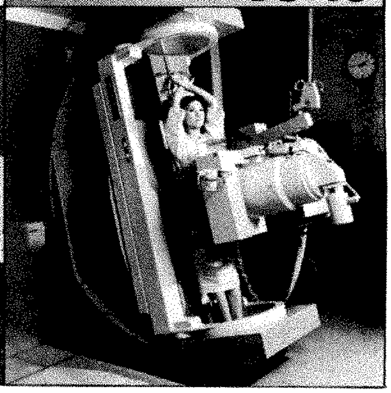

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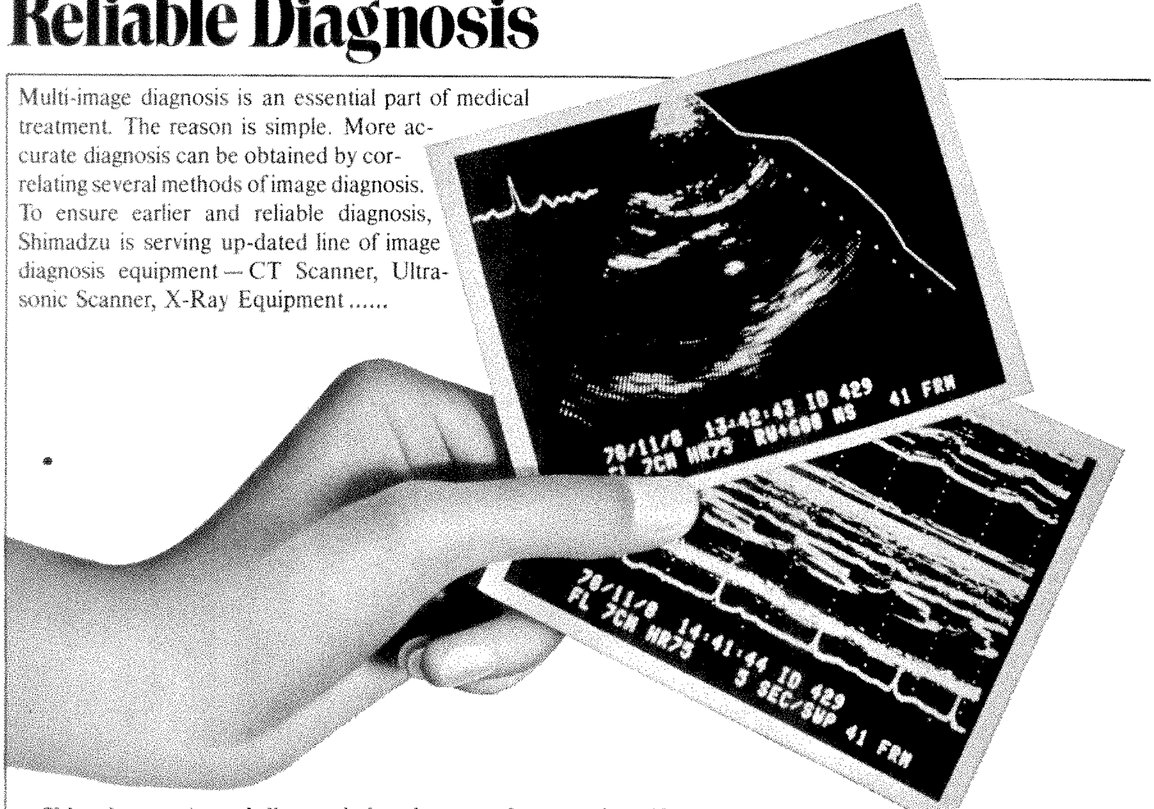

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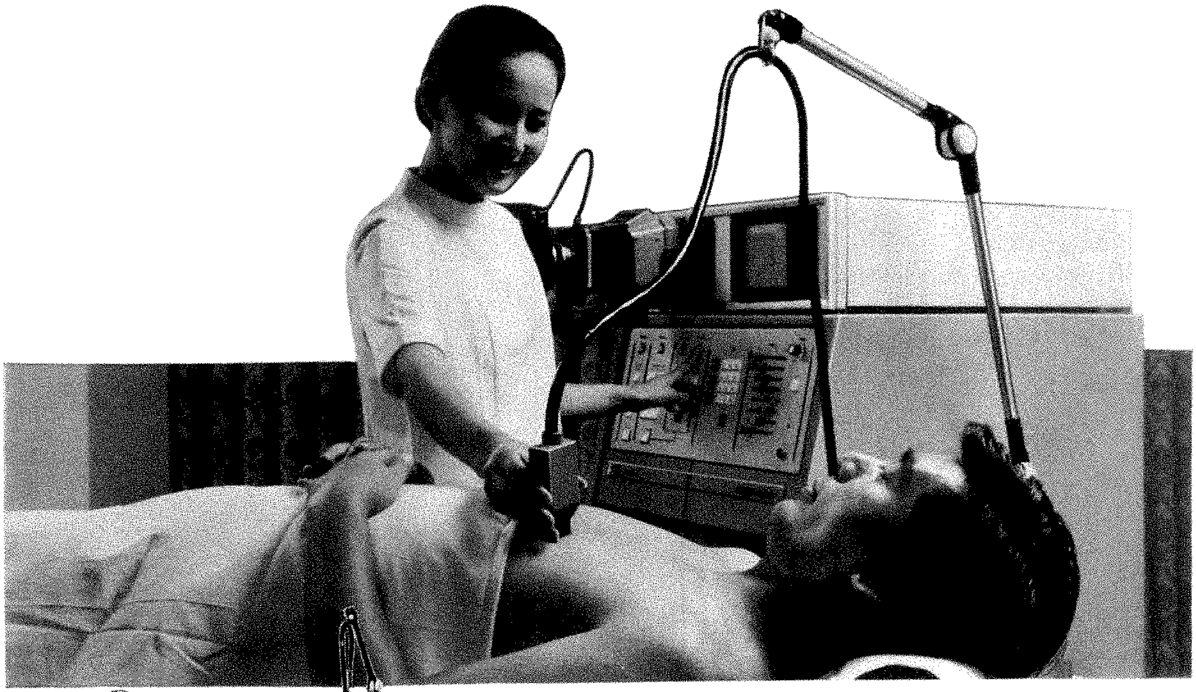

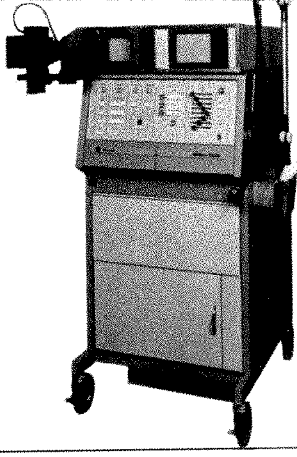

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19–21st September 1979

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Further information can be obtained from Dr. Steiner, Sheffield Children's Hospital, Tel. (0742) 71111.

Application forms and programmes from:

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Trent Regional Postgraduate Committee,
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Conditions of Appointment and Application Forms are available from

The High Commissioner for New Zealand, New Zealand House, The Haymarket, London W.C.2 England.

Applications close at noon on Friday, 28 September, 1979

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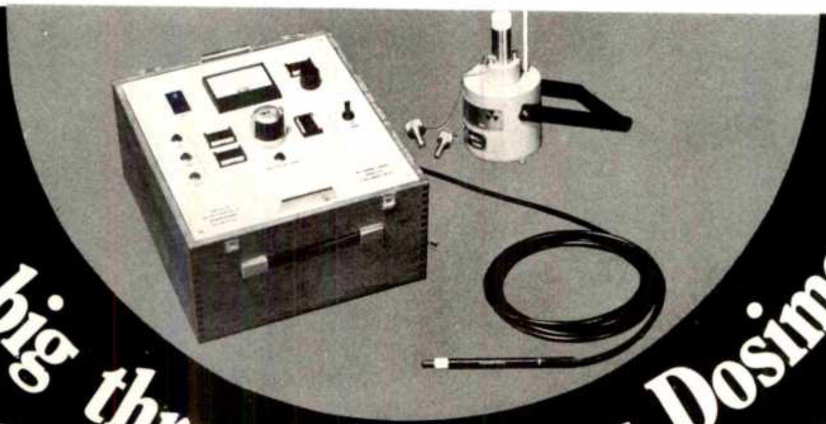
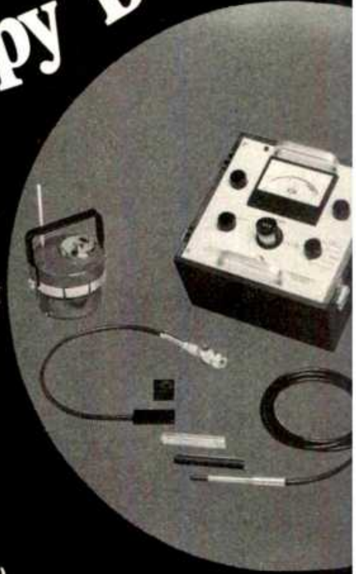
A course on the theory and practice of echocardiography will be held at Freeman Hospital from 17th to 21st September 1979. This is the autumn session of the bi-annual teaching course run jointly by Freeman Hospital and Harefield Hospital. It is intended for physicians, cardiologists, radiologists and senior technicians who have some experience of practical echocardiography, and deals with all the applications of the technique in acquired and congenital heart disease.

The co-chairmen are Dr. Ronald Pridie and Dr. Stewart Hunter and speakers will include Dr. D. Gibson, Mr. G. Leach and Dr. J. Wilkinson. The course is residential and applications should be directed to Dr. S. Hunter, Consultant Paediatric Cardiologist, Ward 7, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne, NE7 7DN (Tel. 0632 843111, ext. 3146) by 18th August 1979.





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over energy range 10kV to 35MV.

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IONEX 2500/3 (Left)
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needs of the therapy department both at therapy and protection levels. Provides dose, doserate, current and charge measurements. Digital display provides up to 999 reading with over range to 1999. Dose from 1mR (1000digit
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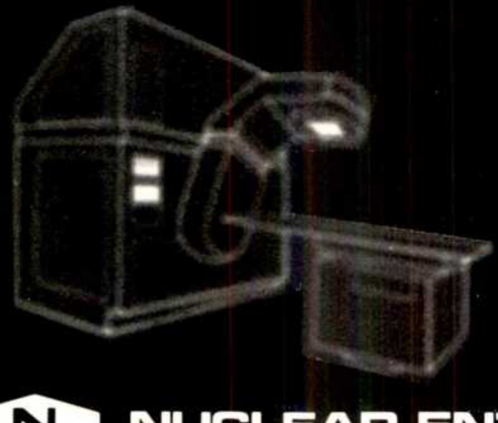

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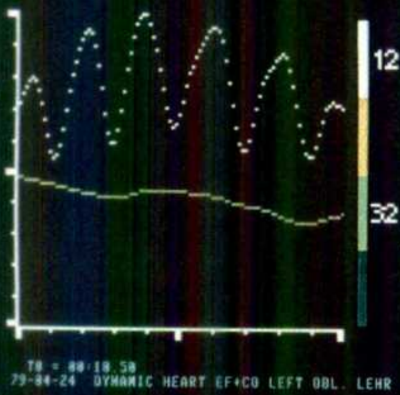

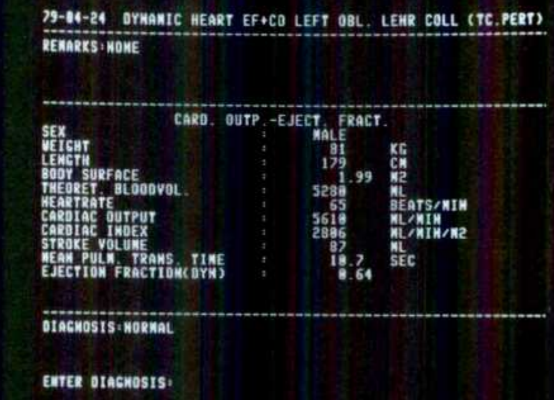

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79-04-24  DYNAMIC HEART EF+CO LEFT OBL. LEHR COLL (TC.PERT)
---------------------------------------------------------------
REMARKS:NONE


---------------------------------------------------------------
              CARD. OUTP.-EJECT. FRACT.
SEX                          :      MALE
WEIGHT                       :        81    KG
LENGTH                       :       179    CM
BODY SURFACE                 :         1.99 M2
THEORET. BLOODVOL.           :      5280    ML
HEARTRATE                    :        65    BEATS/MIN
CARDIAC OUTPUT               :      5610    ML/MIN
CARDIAC INDEX                :      2806    ML/MIN/M2
STROKE VOLUME                :        87    ML
MEAN PULM. TRANS. TIME       :        10.7  SEC
EJECTION FRACTION(DYN)       :         0.64

---------------------------------------------------------------
DIAGNOSIS:NORMAL


ENTER DIAGNOSIS:
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Processing and visualization of the nformation gained by the latest isotope nvestigation techniques, using the amma camera, no longer demands xtensive operational or programming kills. The Philips Processing and Display ystem offers extensive functional lexibility and operational simplicity.

This system combines a Philips mini-omputer (16 bit memory) with disc perated software, but can be operated ven by paramedical personnel to rovide a wide range of completely pre-rogrammed procedures. More involved onfigurations of the standard programs re of course available to the specialist perator due to the free programming acility.

Standard programs that are at presen available include: kidney, brain, heart, lung, liver, pancreas and various others, such as total body, movie, zoom, filter, mono-exponential fit, gamma fit, spline fit, etc.

Application of these programs and of the system's extensive data storage facilities thus guarantees instant exchange of data between departments without the need for time-consuming consultations.

If you would like further information concerning the Philips Processing and Display System please contact: Philips Medical Systems Division, Building QM, Room 351, Eindhoven, the Netherlands

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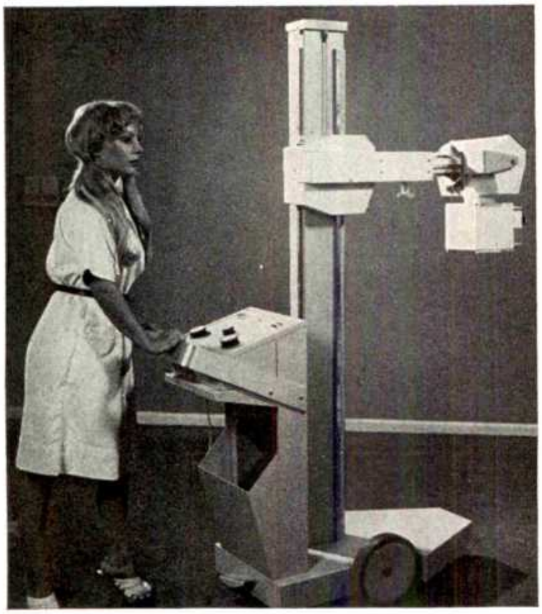
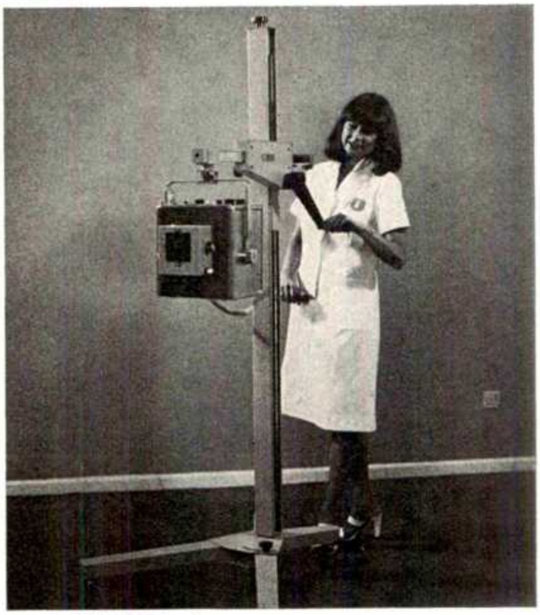
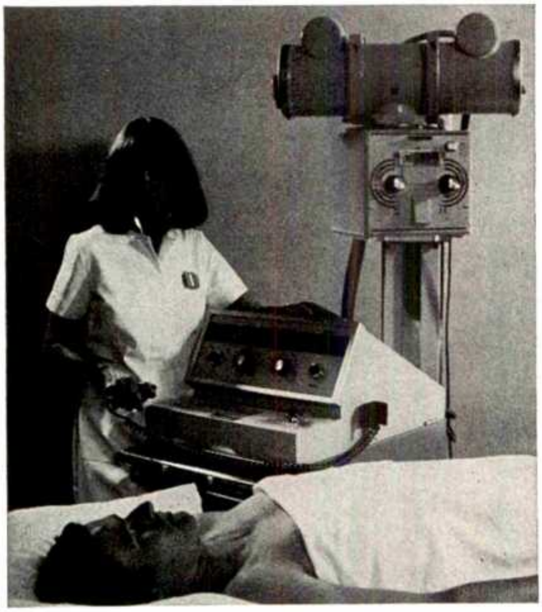


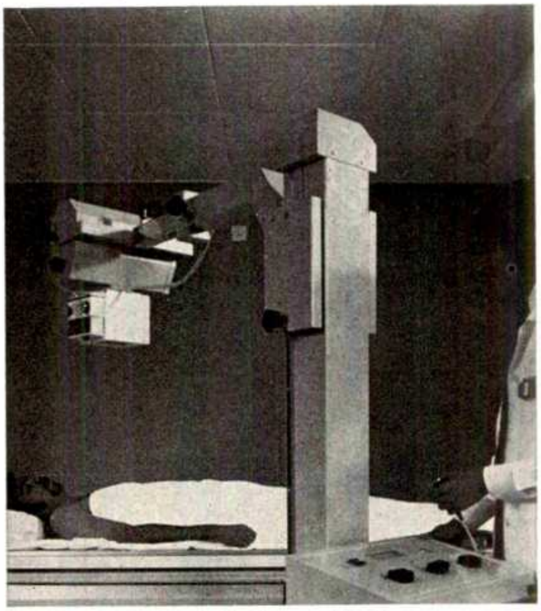
TR 100kV/70mA



TR 100kV/30mA



Condenser discharge units up to 600mAp



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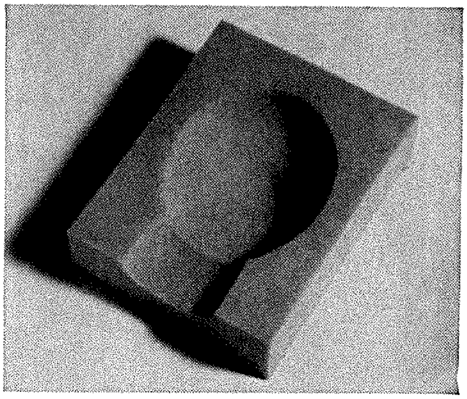

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Radiation Oncologist

Cancer Control Agency of British Columbia

Applications are invited for a full-time post as a Radiation Oncologist to the Cancer Control Agency of B.C. to be based at the A. Maxwell Evans Clinic in Vancouver, B.C. The Agency is affiliated with the University of British Columbia.

The position will involve extensive clinical research participation in the developing pi meson project and clinical and laboratory research in other aspects of radiation oncology.

The Cancer Control Agency sees approximately 4,750 new patients per annum and approximately 4,500 patients per annum receive radiotherapy. The extensive facilities at the Vancouver clinic are in the process of expansion and the radiotherapy equipment includes superficial and orthovoltage X-ray units, four cobalt units, two linear accelerators, one with an electron beam, two simulators, a C.T. scanner and treatment planning computer, radium and other isotopes and a remote handled afterloading low dose rate caesium unit. In collaboration with the B.C. Cancer Research Centre and TRIUMF, the Agency is responsible for the clinical investigation of pi meson therapy and may have isocentric neutron beam therapy from a 42 MeV Cyclotron in the early 1980s.

A number of research projects are under way and with the expansion of the Agency facilities and additional laboratory space in the adjacent Research Centre, the opportunities for further research are excellent. Applicants should have demonstrated research expertise and be interested in furthering an academic career in Radiation Oncology. A specialist qualification in radiotherapy is required and candidates should hold or be eligible to sit the F.R.C.P.(C) in Therapeutic Radiology.
Salary range $44,000.00–$64,000.00 per annum.

Application forms and further information may be obtained from: **Dr. S. M. Jackson, Head of Radiation Oncology, Cancer Control Agency of British Columbia, 2656 Heather Street, Vancouver, B.C., Canada, V5Z 3J3.**

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Micropaque DC represents a significant advance in formulation and production of barium for double contrast work. Using existing CO_2 tablets Micropaque DC provides a medium for excellent definition of detail and it only takes a minute to prepare.

All essential requirements have been built into the pack. It is light in weight, can be held in the hand easily and resealed to reduce wastage.

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Micropaque DC reduces preparation time for the busy radiographer, no pre-mixing or mechanical agitating.

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Micropaque DC

(Barium Sulphate 100% w/v)

Presentation

A low viscosity white suspension containing 100% w/v of barium sulphate with a bland taste and particularly suited to the Double Contrast Technique.

Uses

Radiological investigations of the gastro-intestinal tract.

Doses and Administration

The volume of Micropaque DC used will depend on the patient, the procedure and technique involved. The following dosages represent a basic guide to the quantities suitable for routine examinations: Barium Swallow 40-60 ml undiluted. Double Contrast Stomach and Duodenum Examination 100-150 ml undiluted. Follow through small Bowel Examination 150-250 ml undiluted. Barium Enema 250-500 ml diluted with 500-1000 ml water.

Contra Indications Warnings etc.

Perforation of any region of the gastro-intestinal tract and intestinal obstruction. Pyloric stenosis might be considered as contra-indications to the use of barium sulphate.

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Shake well before use. Store at room temperature. Do not freeze. A light brown supernatant layer may appear and is quite normal. It will disappear when the bottle is shaken.

Legal Category

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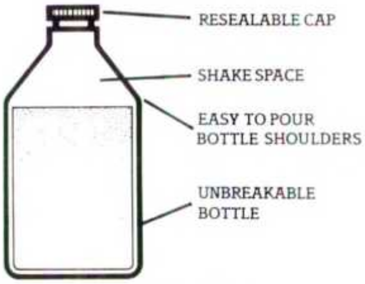
300 ml plastic bottle containing 250 ml suspension and 50 ml 'shake space'. 15 bottles in each pack.



Further Information

Micropaque DC., having a high density combined with a low viscosity, has been formulated to demonstrate particularly fine definition in conjunction with a suitable effervescent distending agent for Double Contrast Technique in the gastro-intestinal tract.

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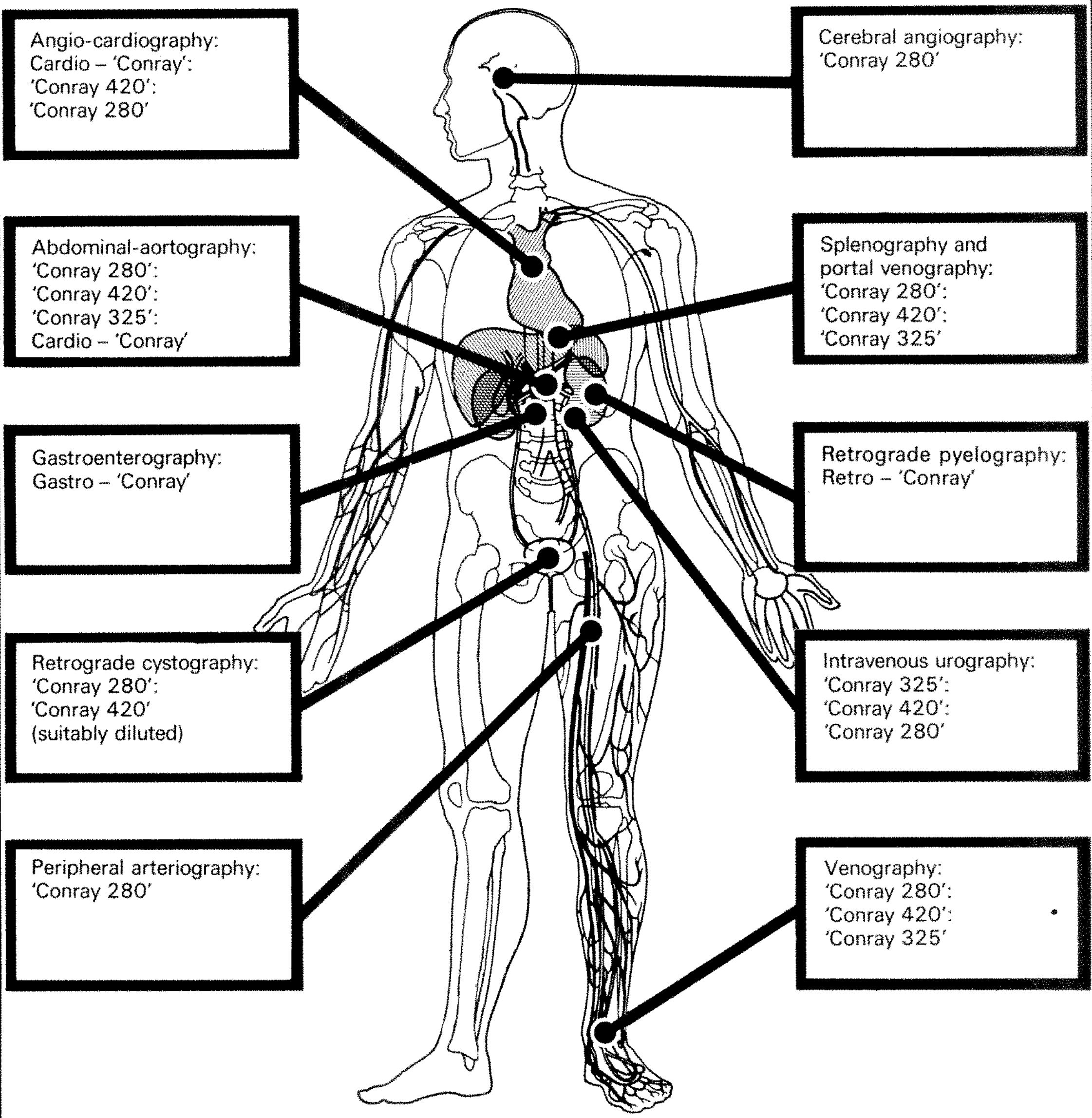

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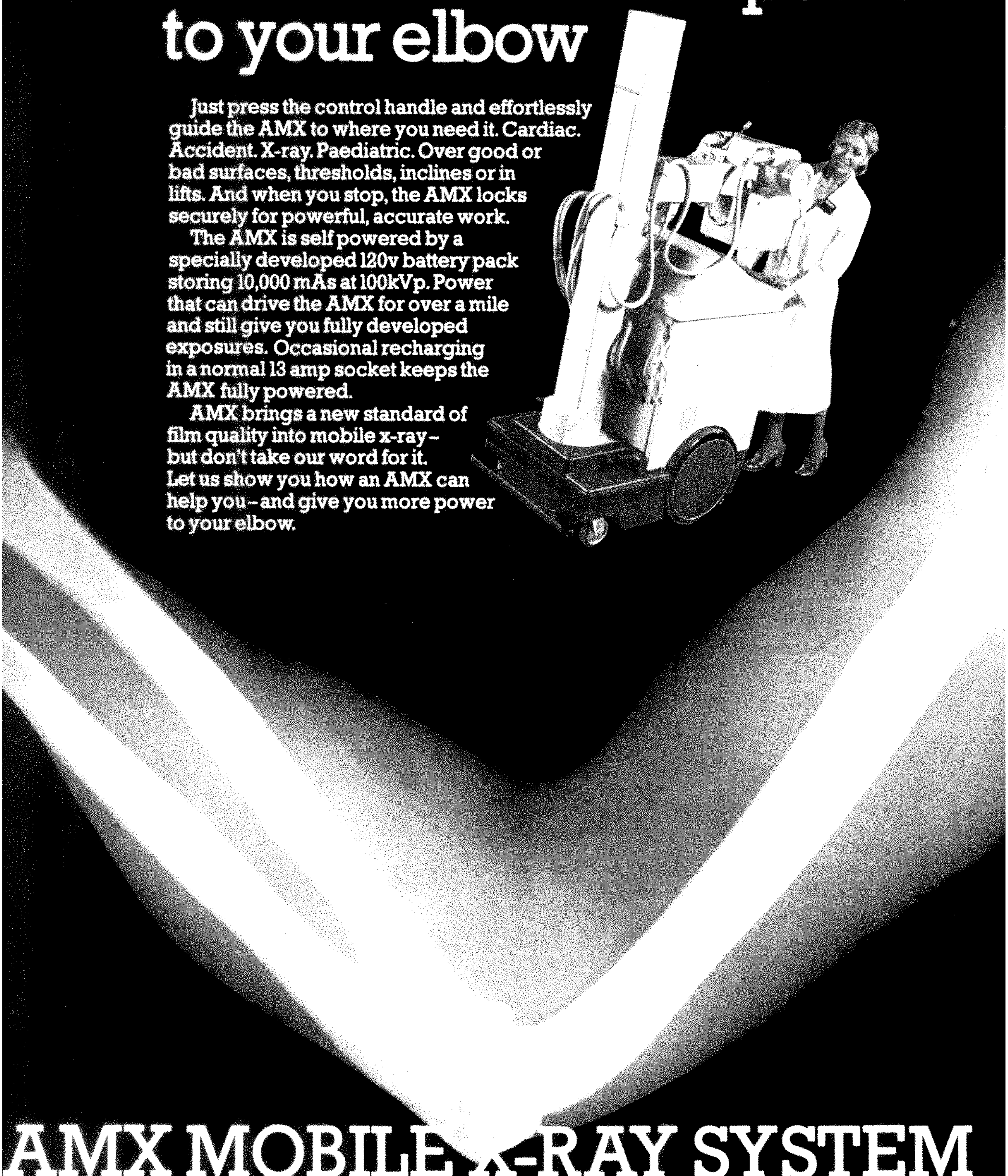

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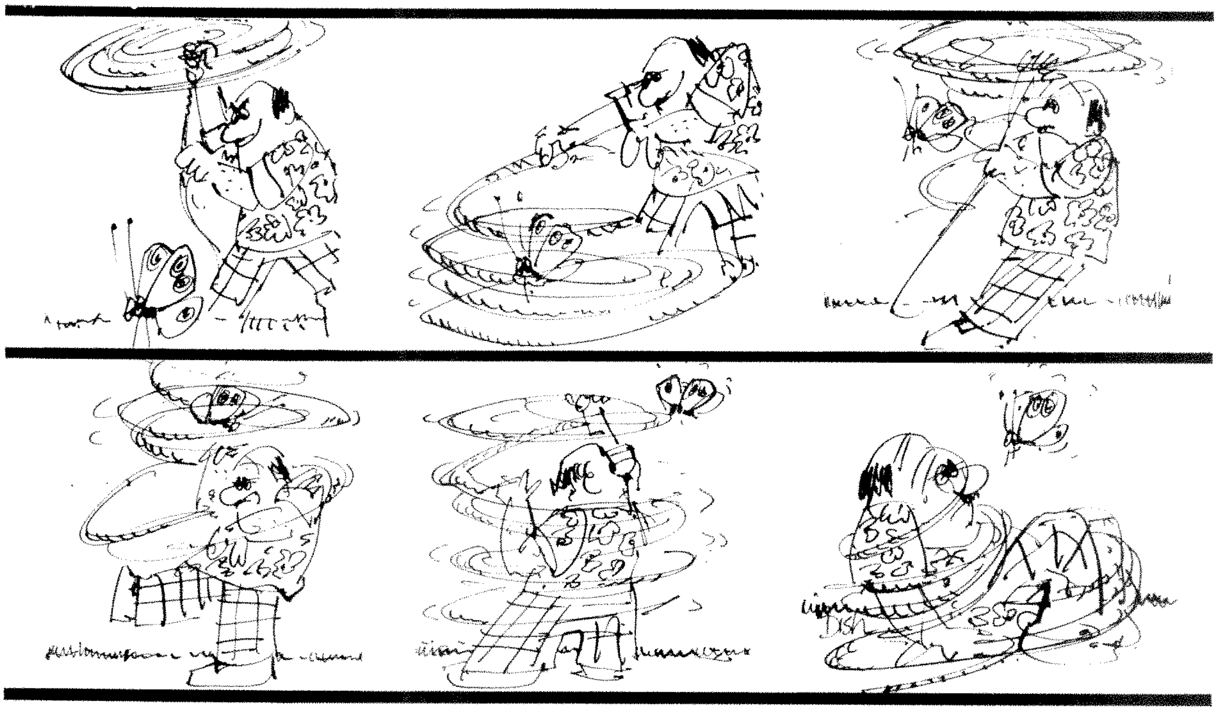

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In fact it's about as difficult as trying to record grey scale detail on high contrast film. Until now only high contrast films have been available for recording Nuclear Medicine, C.T. Scan and Ultrasound images even though the latter does contain subtle grey scale detail. At ILFORD we realized just how difficult this situation could be and so, being experts in image recording, we did something about it.

The results of our research are two new films each designed for its own specific purpose. ILFOSCAN (SP422X) a relatively high contrast film for Nuclear Medicine and C.T. Scanning applications and ILFOSOUND (SP440X) for recording the grey scale detail of Ultrasound. These two films are the sensible solution to a serious problem. In short, two nets where a lasso wont do.

After all, who enjoys being tangled up in their work.

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ILFOSCAN (SP422X) The film for Nuclear Medicine and CT Scanners.

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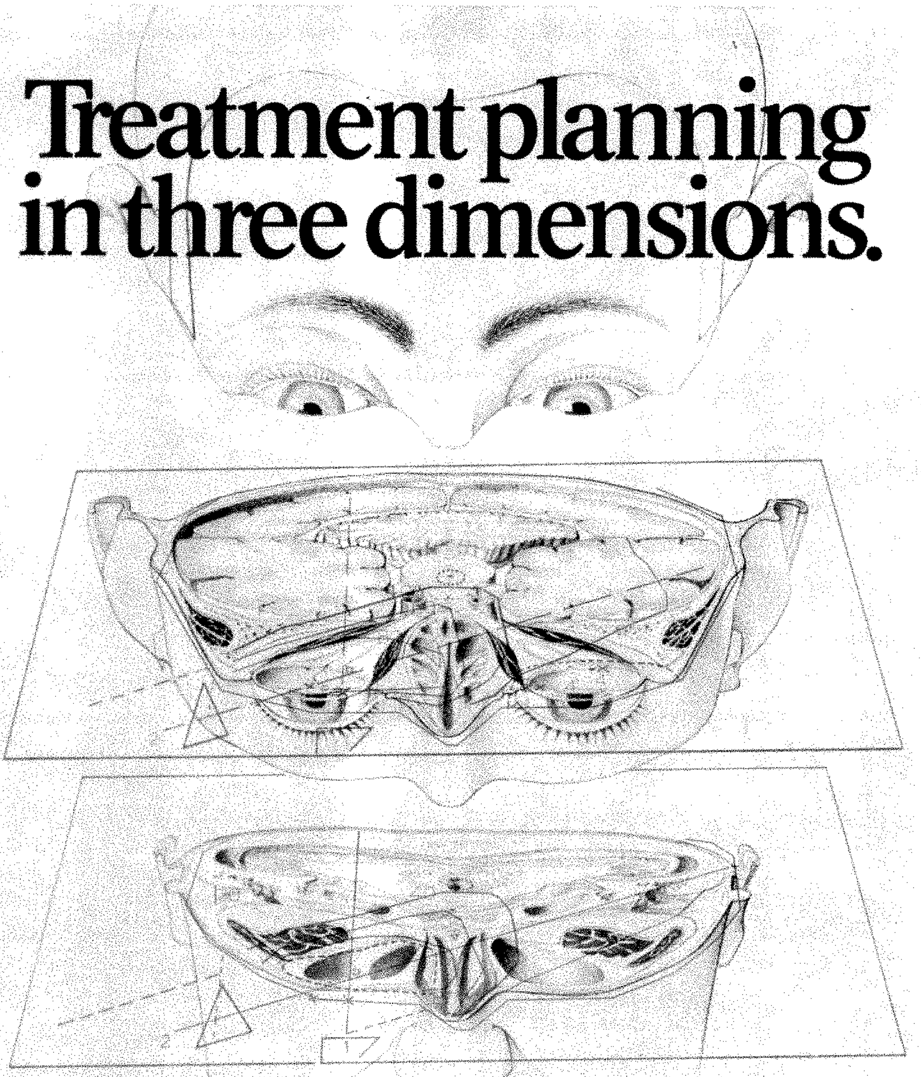
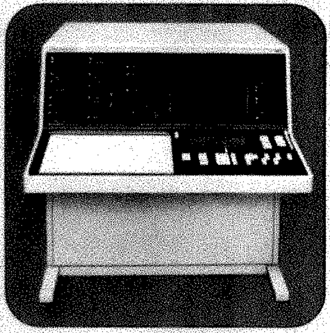


Treatment planning in three dimensions.



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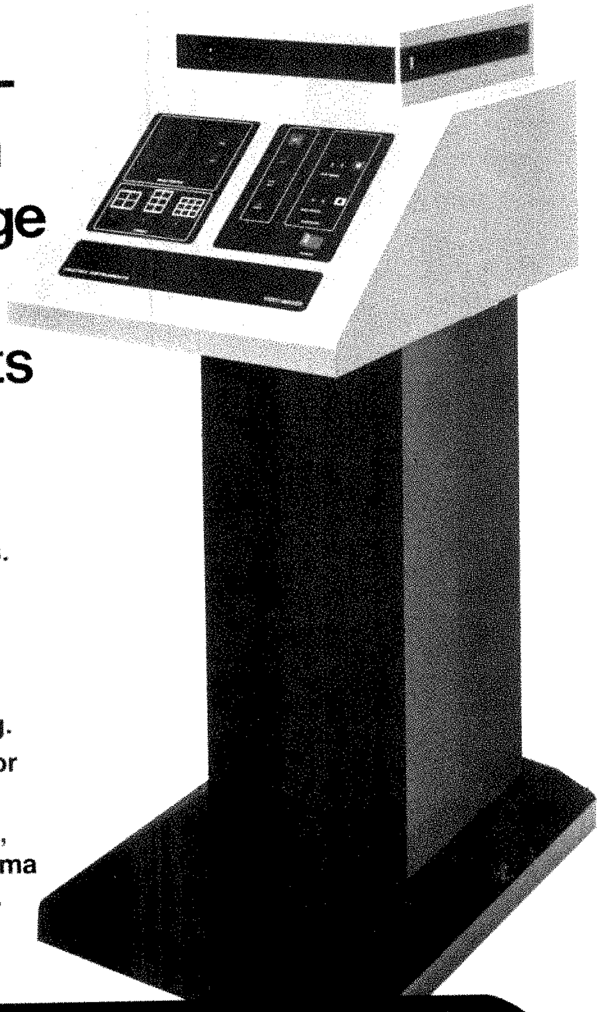

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NOTICE

The 5th CARVAT: International meeting on body CT, organized and directed by Prof. P. Rossi and Prof. R. Passariello, will be held in Rome from May 19 to 23, 1980 at the Hilton Hotel.

The programme of the meeting is based on whole body CT clinical applications, with the exception of brain scanning.

Proposed papers by the participants will be accepted, after evaluation.

Lectures will be given by American and European guest speakers:
H. Abrams, R. Alfidi, A. Baert, E. Boijsen, L. Di Guglielmo, W. Fuchs, M. Geindre, L. Jeanmart, I. Isherwood, L. Kreel, J. L. Lamarque, L. Oliva, C. Pedrosa, G. F. Pistolesi, U. Salvolini, U. Scherer, A. van Voorthuisen, S. Wallace.

Official languages will be English and Italian with simultaneous translation.

Any request of information may be sent to:
Prof. Plinio Rossi—Istituto de Radiologia—Policlinico Umberto I—00161 Rome (Italy)

Secretary: Dr. G. Simonetti

The British Institute of Radiology

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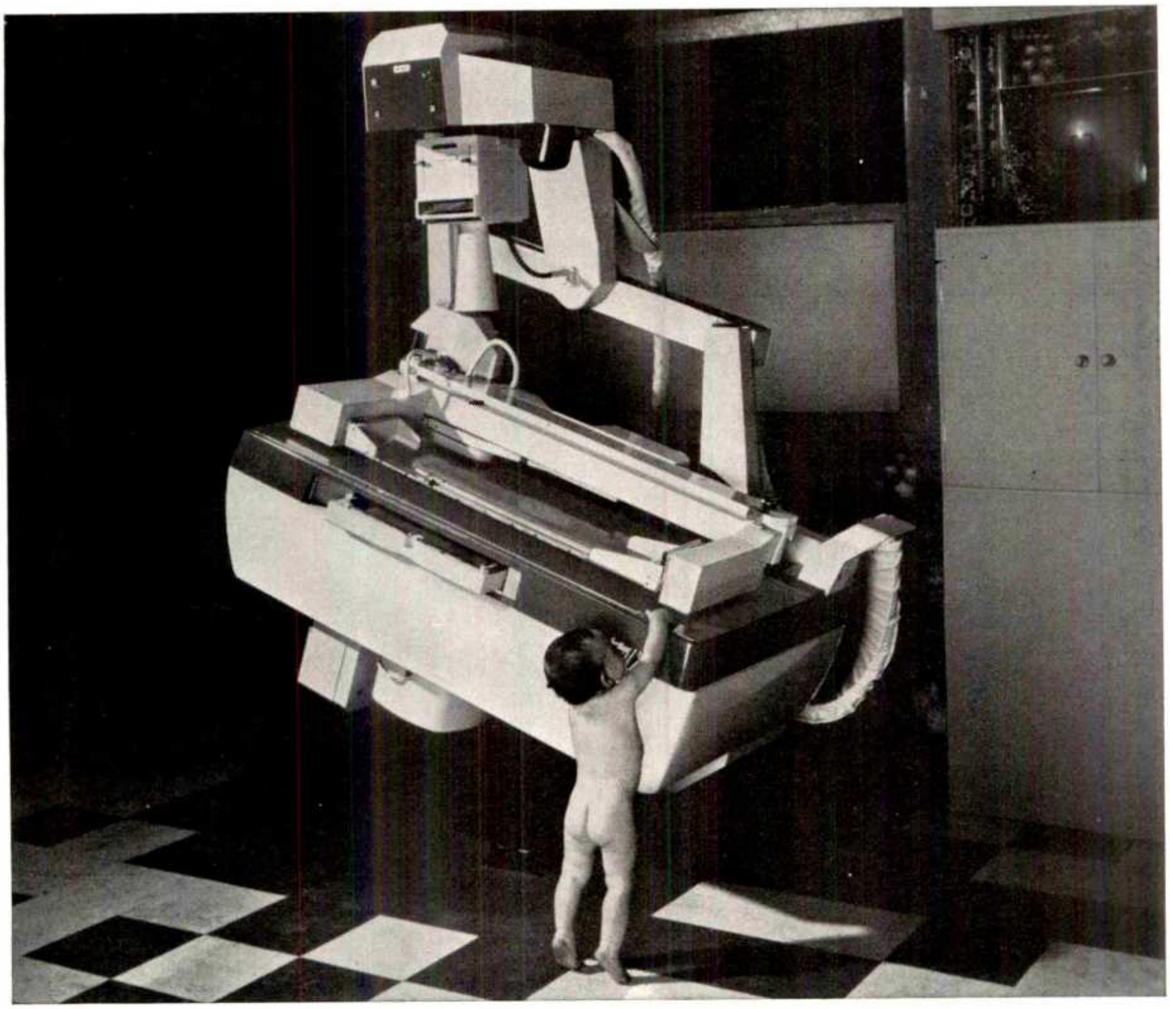
A table designed specifically for all infant radiological investigations



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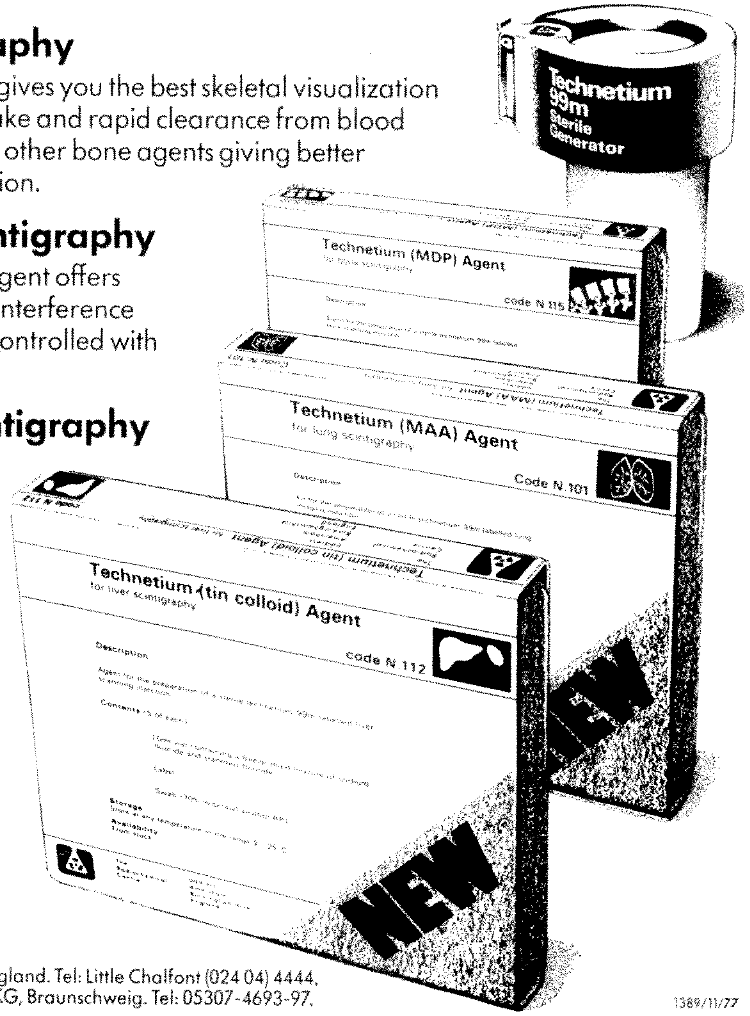

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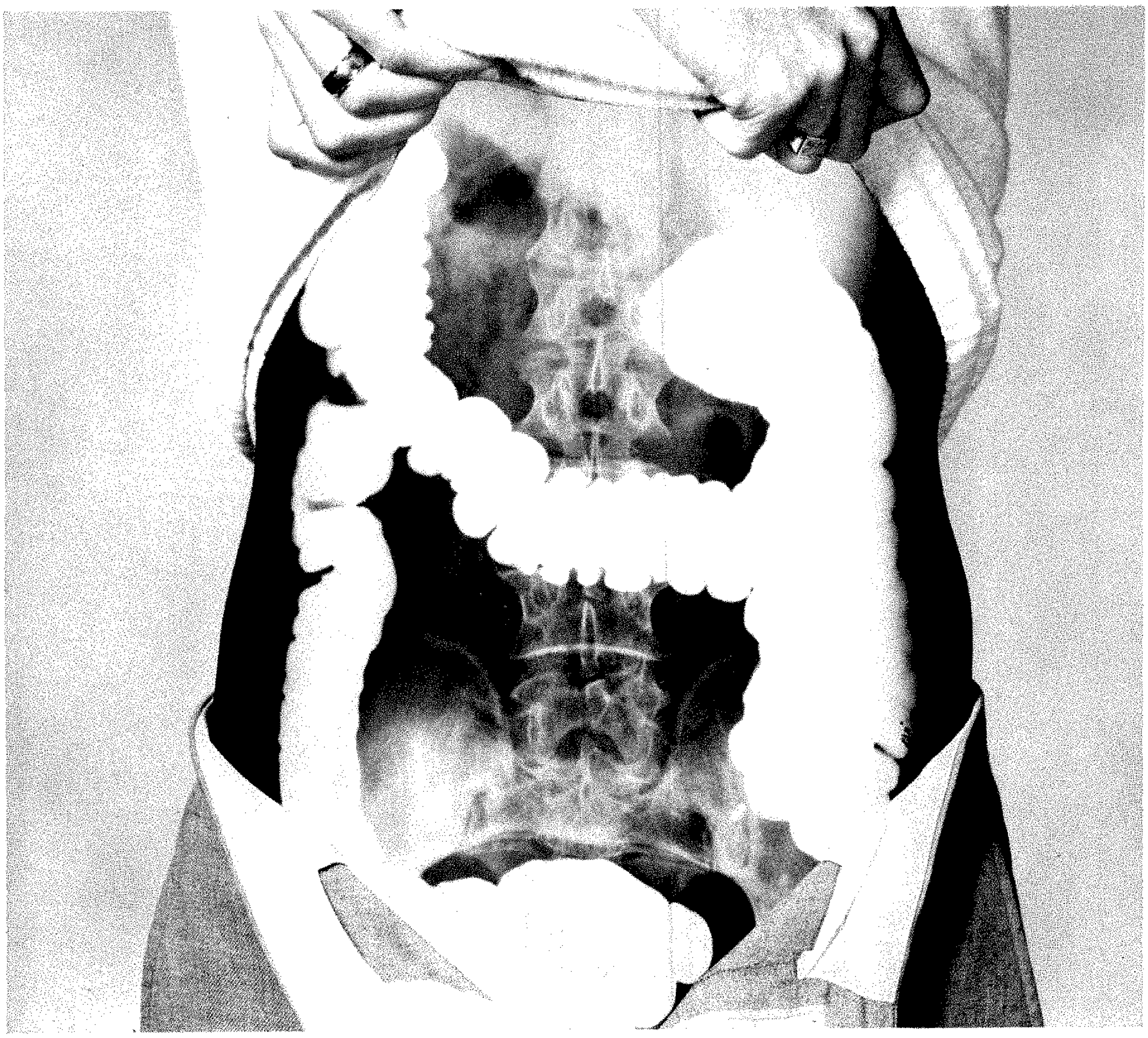

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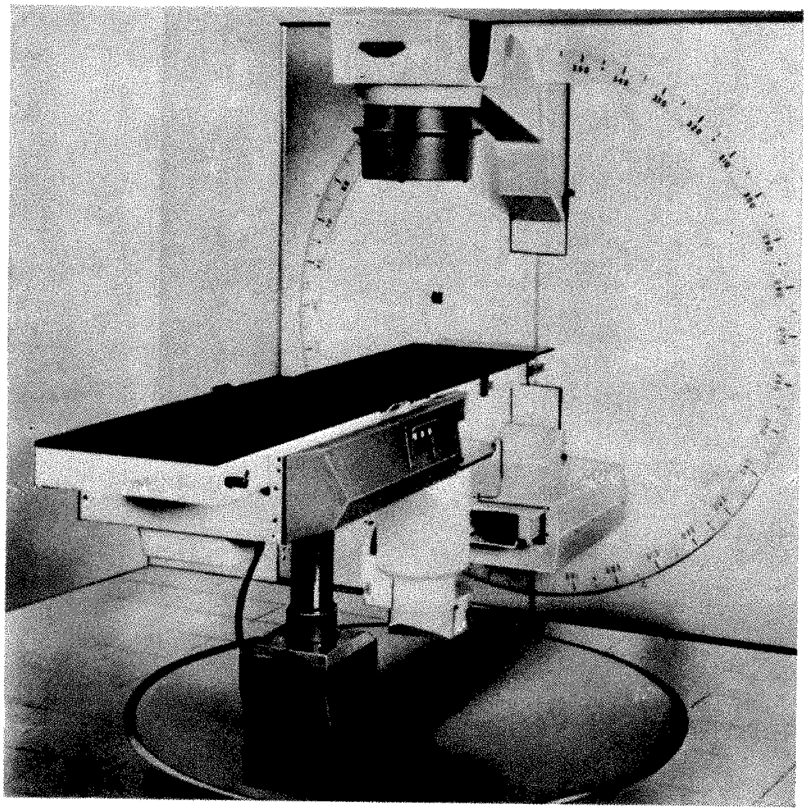

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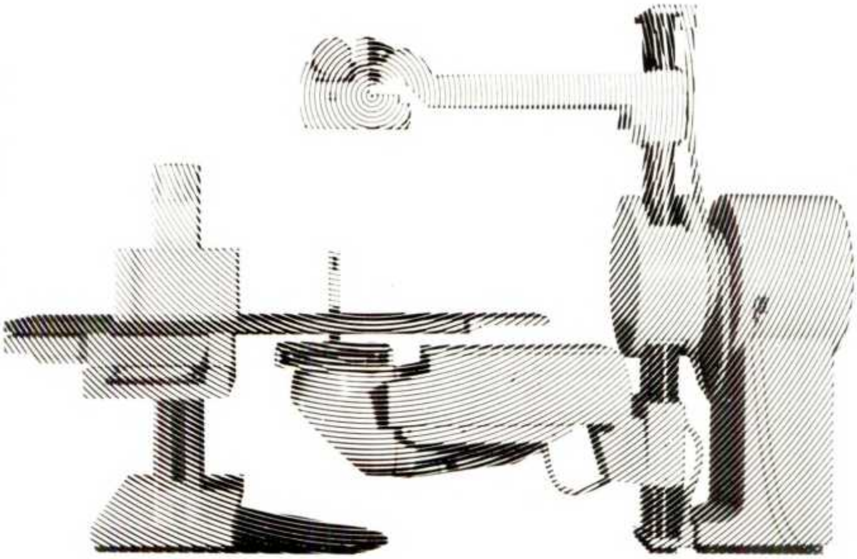

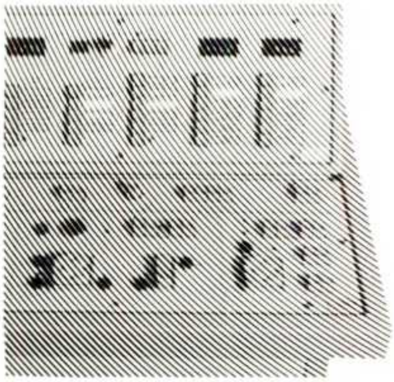

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1979, *British Journal of Radiology*, 52, 605–607
VOLUME 52 NUMBER 620 AUGUST 1979

The British Journal of Radiology

Radiology now

Radionuclide investigations and pregnancy — protection of the embryo and fetus

The application of the "ten-day principle" which recommends that radiological examinations of the lower abdomen of women of reproductive capacity should be restricted to the ten day interval following the onset of menstruation (ICRP, 1977), has been discussed recently in relation to diagnostic radiology by Carmichael and Warrick (1978). However, these authors did not discuss the application of the principle in diagnostic investigations involving administration of radionuclides to the patient.

The question of whether the ten-day principle should be applied to investigations involving the administration of radiopharmaceuticals is a complex issue. In contrast to investigations involving X rays, where the radiation dose is delivered over a period of seconds or minutes, administration of radiopharmaceuticals results in prolonged irradiation over periods which may range from minutes to months, depending on the effective half-life of the radiopharmaceutical. Further, in the case of X rays, application of the ten-day principle prevents any irradiation of an embryo, whereas administration of a radiopharmaceutical may result in irradiation of an embryo if fertilization occurs after the radionuclide investigation has been completed, but before all the activity has disappeared. In attempting to assess the risks of fetal damage or childhood malignancy arising from radiopharmaceutical administration it is necessary to consider the effects of prolonged exposure of concepta of various ages to radiation at low dose rates. At present there is very little good experimental information on these effects and it is difficult to make a well balanced scientific judgement of the risks of embryonic or fetal damage.

Advice on the application of the ten-day principle to women undergoing investigations with radiopharmaceuticals has been published by Ellis *et al.* (1977) who classified subjects into three groups.

(a) Volunteers acting as controls in research studies.
(b) Patients participating in research investigations relevant to their clinical condition but not strictly necessary for their management.
(c) Patients undergoing investigations required for their proper management.

They recommended that for subjects in category (a) the ten-day principle should be applied strictly for all radiopharmaceutical investigations. For patients in categories (b) and (c) it was suggested that the principle need only be considered for radionuclide investigations which give gonad doses in excess of 50 mrem (500 μSv) and have effective half-lives short compared to ten days. The value of 50 mrem (500 μSv) was chosen as corresponding to category I of the WHO expert committee (WHO, 1977). For radiopharmaceuticals with effective half-lives long compared with ten days the ten-day principle was considered to be of "little relevance".

These recommendations have been severely criticized. Croft and Maisey (1978) point out that some evidence suggests that irradiation of the unfertilized ovum may be as dangerous as irradiation of an early embryo or fetus. They suggest that if this view is upheld, it is illogical to apply the ten-day principle without also advising the patient to avoid becoming pregnant for a period long enough to allow repair of radiation damage. These authors also draw attention to the apparent double standard in the recommendations of Ellis *et al.*, that the principle should be applied only to radiopharmaceuticals with short effective half-lives. Langmead (1977) suggests that the ten-day principle should apply to all investigations where the total gonad dose exceeds 50 mrem, irrespective of the effective half-life of the radiopharmaceutical, and that the patient should be advised to avoid pregnancy for a period of three to four times the effective half-life of the particular radiopharmaceutical.

Sear (1978) has questioned the limit of 50 mrem for the application of the "ten-day principle", suggesting that this dose is too low to be a suitable criterion for the application of the rule and that a dose of 0.5 rem would be more appropriate.

Any objective re-appraisal of the application of the ten-day principle in nuclear medicine should consider the following questions.

(a) Should the ten-day principle apply to any administration of a radiopharmaceutical?
(b) If so, should it apply to all diagnostic or investigational procedures?
(c) Is there a lower limit of radiation dose below which the rule need not apply?
(d) Should the subject be advised to avoid pregnancy for a period after the investigation?

The most up-to-date review of the effects of radiation on the developing embryo and fetus is contained in the UNSCEAR Report (1977). This highlights the almost complete lack of information on the effects of internal radiation, or of prolonged external exposure at low dose levels.

With our present very limited knowledge of the effects of low doses of radiation on the developing embryo and on the unfertilized ovum, it would appear wise to apply the ten-day principle to all radiopharmaceutical investigations irrespective of their effective half-lives.

The question of a lower dose limit below which the "ten-day principle" need not apply is very difficult to answer in view of the dearth of relevant information. In these circumstances it seems most reasonable for the purpose of risk assessment to assume that the relationship between radiation dose and unacceptable damage to the embryo and fetus is stochastic, that is without a threshold, linear and independent of dose rate.

Although there are insufficient data on the effects of low levels of internal irradiation *in utero* to make a realistic risk estimate, there are sufficient data from studies of the effects of external radiation to suggest a "tentative upper limit of risk", which might be useful to the clinician who has to make the "risk-benefit judgement".

Mole (1979) has reviewed the data on pre-natal irradiation and concluded that the overall risk of induction of malformation or cancer lies in the range $0-1\times10^{-3}$ rem^{-1} ($0-1\times10^{-1}$ Sv^{-1}). Assuming a risk of 10^{-3} rem^{-1}, then for a 50 mrem (0.5 mSv) dose, the dose level suggested by Ellis *et al.* (1977), the additional risk would be around 1 in 20000.

In the case of a mother whose pregnancy was unknown at the time of administration of a radiopharmaceutical, significant irradiation extending into the fetal period would occur only with radiopharmaceuticals having a long effective half-life, for example ^{75}Se-selenomethionine. These extra risks are small compared to the risk of severe handicap arising from natural and environmental factors, which is estimated, for the average pregnancy, as about 1 in 30 (Mole, 1979). To raise the gonad dose limit to 500 mrem (5 mSv), which would exempt the majority of current radionuclide investigations from the need to apply the ten-day principle, would raise the tentative upper limit of risk for malformation to 1 in 2000, a level which is more than sixty times less than the natural risk of malformation or malignancy.

The avoidance of pregnancy for a period after administration of a radiopharmaceutical in order to reduce the risk of irradiation of a new embryo from the retained radionuclide, or to allow repair of radiation damage, would be a sensible precaution, especially if the higher limit of 500 mrem (5 mSv) for the application of the ten-day principle is accepted. There is, as yet, no direct evidence that the irradiated human ovum can repair non-lethal radiation damage; however, studies of DNA repair mechanisms in mammalian cells suggest no *a priori* reasons why human germ cells should not be capable of effecting non-reduplicative repair.

For most radiopharmaceuticals in routine use a period of two months would allow good time for repair processes to occur without placing undue restriction on the patient. Investigations involving ^{75}Se-selenomethionine, which has an effective half-life for the whole body of 63 days (ICRP, 1971), would place a more severe restriction on the patient who would have to be advised to avoid pregnancy for about nine months.

In conclusion, the recommendations of Ellis *et al.* (1977) concerning the application of the "ten-day principle" in nuclear medicine appear to be unnecessarily restrictive and the following revised recommendations are proposed.

1. That the "ten-day principle" should be applied to all diagnostic radiopharmaceutical investigations in which the calculated gonad dose exceeds 500 mrem (5 mSv) (WHO, category II) unless there are over-riding clinical reasons for carrying out the investigation as an urgent procedure.

2. That when the gonad dose exceeds 500 mrem (5 mSv), the patient be advised to avoid becoming pregnant for a period of two months, or four times the effective half-life of the radiopharmaceutical if this time is longer than two months, following the investigations.

3. That for all volunteers in research investigations the "ten-day principle" should be applied

strictly in all cases when the gonad dose exceeds 50 mrem (500 μSv) (WHO category I).

These revised recommendations, in contrast to those of Ellis *et al.* (1977), do not distinguish between investigations which are essential for the proper management of the patient and those which while relevant are not strictly necessary. The higher limit on the gonad dose which is now proposed would appear to carry an additional risk of unacceptable malformation or of childhood malignancy which is much less than the natural risk of such hazards. The application of these revised recommendations including the avoidance of pregnancy for at least two months is in full accord with the ICRP requirement to ensure the minimization of exposure to any embryo and fetus (ICRP, 1977).

D. M. Taylor*

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Book review

Radiobiology for the Radiologist. By E. J. Hall, 2nd ed., pp. xiii + 460, illus. 1978 (New York, Harper & Row), $25.00. ISBN 0–06–141074–8

In its second edition this book has been expanded and brought up to date to cover new developments in the subject and changes in the syllabus for trainee radiologists. The book has been reorganized so that the areas of interest to students of radiotherapy, diagnostic radiology and nuclear medicine have been more clearly delineated; each chapter is marked as suitable for one or more of each specialty.

For the diagnostic radiologist the section on carcinogenesis and genetic effects of small doses of radiation has been greatly enlarged, and the book concludes with a chapter attempting to discuss risk versus benefit of diagnostic procedures. This latter is largely theoretical but thought-provoking, for instance the risk of death from the carcinogenic effect of a barium enema is equated with that of smoking 128 cigarettes, or driving 313 miles!

For the radiotherapist the book remains an excellent introduction to the principles of the subject; the effects of radiation at the cellular level are particularly clearly described.

The chapter devoted to fractionation in radiotherapy is disappointing. It is brief, with no discussion of the clinical effects of different fractionation schedules, in contrast to the section on high LET radiation where there is detailed critical discussion of the clinical results of fast neutron therapy. The reader is led to believe that in clinical radiotherapy a fractionated regimen results in more damage to the tumour, because of reoxygenation, than the same total dose given in a single fraction. There follows a description of the NSD and TDF formulae with examples of the application of the latter, introduced by the statement that "the system may be used to design treatment plans which have variable fractionation patterns but which result in comparable biological effects". There is no warning that much animal and clinical data suggest that the formulae may not apply to many normal tissues and cannot safely be used to predict tolerance in all instances when fractionation is changed.

The section on high LET radiation is extended in the light of recent developments, and a completely new section on hypoxic cell sensitizers added to keep abreast of current endeavours to apply radiobiological knowledge to improve results of radiotherapy. In addition there is a chapter on hyperthermia, a subject which, although not strictly radiobiological, is certainly now being studied by radiobiologists and has implications for radiotherapy.

This book was designed to cover the requirements for training of diagnostic and therapeutic radiologists in the United States. It covers most of the radiobiology syllabus for trainees in these specialties in the United Kingdom and can be recommended to them as one of the clearest introductions to the subject.

J. M. Henk.

1979, *British Journal of Radiology*, *52*, 608–619

High definition imaging of carotid arteries using a standard commercial ultrasound "B" scanner

A preliminary report

By B. M. Gompels, M.B., B.S., D.M.R.D., F.R.C.R.

Department of Diagnostic Radiology, Epsom District Hospital, Epsom, Surrey

(*Received January 1979*)

ABSTRACT

Sixteen carotid arteries in nine patients with transient ischaemic attacks and carotid bruits were examined by direct scanning grey scale ultrasound using a 10 HMz probe attached to a standard commercial apparatus. Findings using ultrasound were compared with a contrast arteriogram performed on the following day and, in two cases, with the surgical appearances during endarterectomy.

Atheromatous plaques were demonstrated in five common carotid arteries by ultrasound. Arteriography failed to show proximal plaques in two common carotid arteries and extension of bifurcation disease into the adjacent common carotid in a third patient.

Ultrasound detected four stenotic and one occluded internal carotid artery. One internal carotid artery with a 25% stenosis was shown by arteriography but not by ultrasound. Of the five external carotid stenoses, one with a minimal stenosis of less than 10% was not demonstrated. In all cases, stenoses in excess of 30% were shown by ultrasound.

Surgical findings correlated more closely with details of the plaques as shown by ultrasound than by arteriography. It is suggested that ultrasound might be used to preselect reliably those patients who would benefit from a contrast arteriogram and, thus, to protect those with normal carotid arteries from a potentially hazardous invasive investigation.

Major cerebro-vascular episodes, often preceded by transient ischaemic attacks, are frequently related to extra-cranial arterial occlusive disease. In most centres, contrast arteriography is used to indicate the site and distribution of atheromatous plaques and stenoses in the carotid arteries, but it is an invasive technique, potentially hazardous, and may underestimate the extent of arterial pathology. During the past decade, considerable interest has been directed towards developing non-invasive methods of investigating these patients.

Many forms of non-invasive investigations are currently in use but all ultimately have limitations. For example, bruits which may be heard over the carotid bifurcation can visually be analysed by phonoangiography. However, a loud bruit may be present with minimal stenosis (McRae and Kartchner, 1978) and the reduced blood flow associated with an internal carotid stenosis in excess of 80–90% may be inadequate to cause a bruit. Despite these limitations, carotid phonoangiography identifies bruits related to a significant stenosis and can differentiate noises transmitted from the chest. Ocular plethysmography assesses the timing of the ocular arterial pulse and is helpful in gauging the functional significance of stenotic lesions and the continued patency of a vessel following endarterectomy (Brockenbrough *et al.*, 1967). Ocular plethysmography and carotid phonoangiography combined have an accuracy of 89% in identifying a stenosis of more than 40% (Kartchner and McRae, 1977) and will increase the positive yield of carotid contrast arteriography from 39% to 68% (Kartchner *et al.*, 1976).

The systolic pressure in the ophthalmic artery and calibrated pulse volume changes from the ocular globe may be obtained simultaneously from both eyes by ocular pneumoplethysmography. Gee *et al.* (1976) claim a 100% accuracy in detecting unilateral carotid occlusive or pre-occlusive stenosis although the method becomes less reliable in the hypertensive patient.

Reverse flow in the ophthalmic collateral circulation which occurs in the presence of internal carotid stenosis can be assessed by a Doppler ultrasonic flow detector. However, LoGerfo and Mason (1974) have shown that retrograde flow is not necessarily an index of the clinical significance of a carotid stenosis and will only indicate the presence of a stenosis in excess of 75%. Both continuous wave and pulsed Doppler arteriography will image a 25% stenosis at the bifurcation and differentiate high grade stenosis from occlusion. Mozersky *et al.* (1972) and Barnes (1978) suggest that the examination will be limited when there is calcium in the atheromatous plaque since calcium produces a blank area that cannot be evaluated.

Blue *et al.* (1972) showed a 73% correlation between 2 MHz B-mode ultrasonic scanning and arteriograms in 15 patients in which there were no false negatives. Green (1978) and Mercier *et al.* (1978) have successfully produced high resolution images of the carotid arteries using a 10 MHz transducer with a real-time ultrasound B-scanning facility.

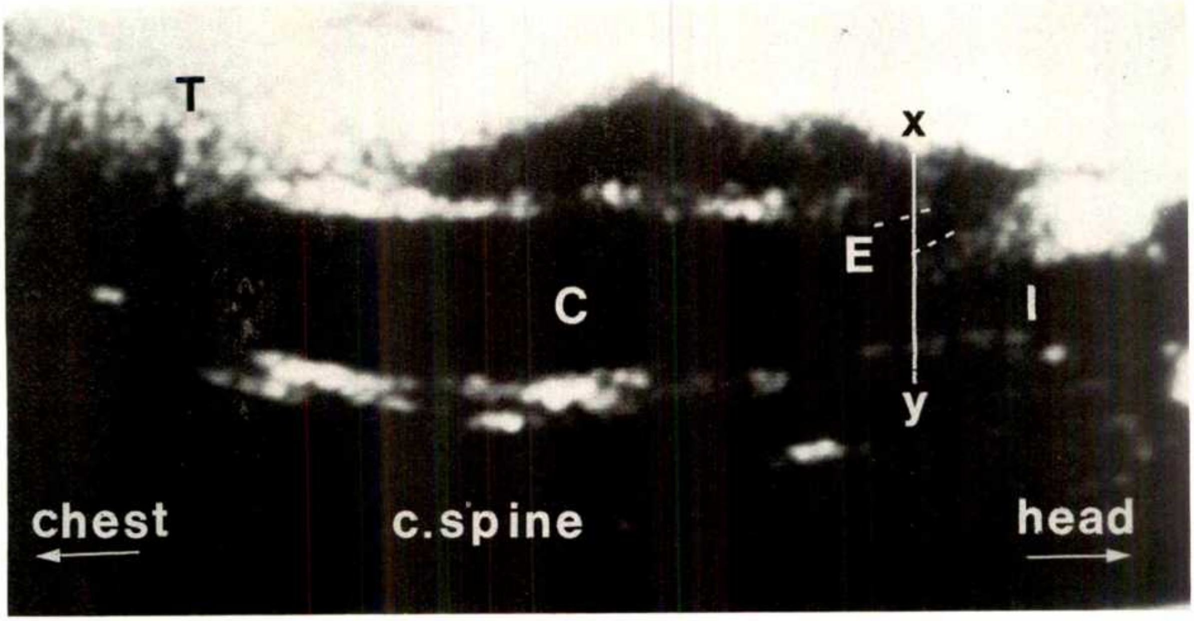

FIG. 1A.

Sagittal section through a normal common carotid and internal carotid artery. Only the proximal 2–3 mm of the external carotid artery is shown as it is lying medial to this sectional plane. The normal carotid artery has a thick wall and smooth intimal lining.
C = common carotid artery, E = external carotid artery, I = internal carotid artery, T = thyroid gland.

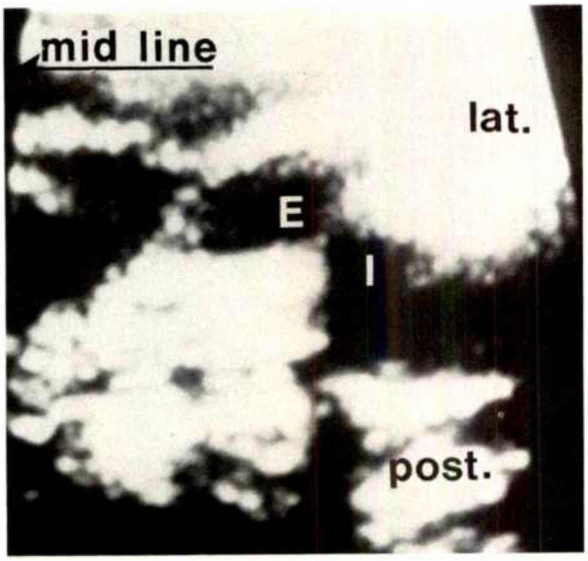

FIG. 1B.

Transverse section through XY of Fig. 1A showing proximal ends of normal internal and external carotid arteries. The external carotid lies antero-medial to the internal carotid and is usually of smaller cross-sectional diameter. Same patient as Fig. 1A. *Orientation:* Right of ultrasound illustration is cephalic to correspond with accepted representation of decubitus carotid arteriogram.

The purpose of this communication is to suggest that reliable results can be obtained with a direct scanning technique using a 10 MHz transducer attached to a standard commercial ultrasound apparatus.

MATERIAL AND METHOD

From January to August, 1978, 80 carotid arteries were examined routinely during thyroid examinations with ultrasound using a 5 MHz transducer in order to perfect scanning techniques for carotid arteries. With the availability of a 10 MHz transducer, this scanning experience was applied to obtain high resolution images in 19 patients with suspected carotid artery lesions during the four month period of September to December, 1978. Only those patients in whom arteriography was performed are discussed in this paper.

Nine patients (16 carotid arteries, including two unilateral examinations), all with transient ischaemic attacks and localized carotid bifurcation bruits, were examined by grey scale ultrasound in the supine position with the head partially extended. Initially the carotid arteries were palpated to assess their course and tortuosity in the neck. A 10 MHz,

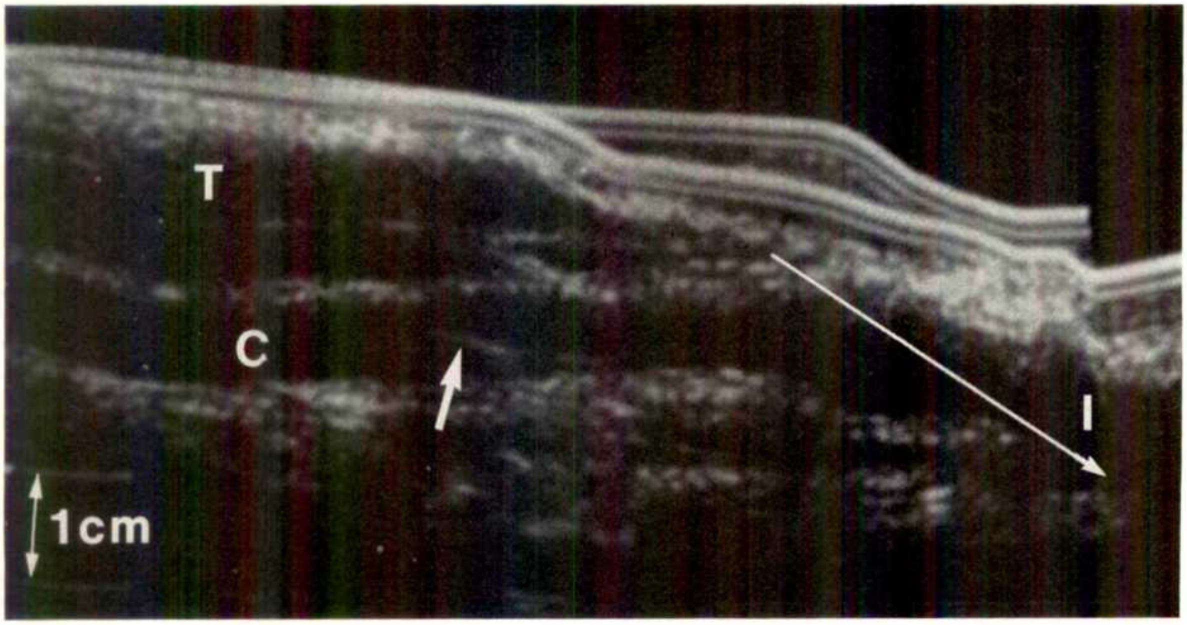

FIG. 2A.

Longitudinal section through the common carotid artery demonstrating an oblique atheromatous plaque (short arrow) attached to the posterior wall of the artery about 2 cm proximal to the origin of the internal carotid artery. The long thin arrow represents the cannula as shown in Fig. 2B. Note normal posterior deflection of the internal carotid artery position in relation to the common carotid artery.

C = common carotid artery, I = internal carotid artery. T = thyroid gland.

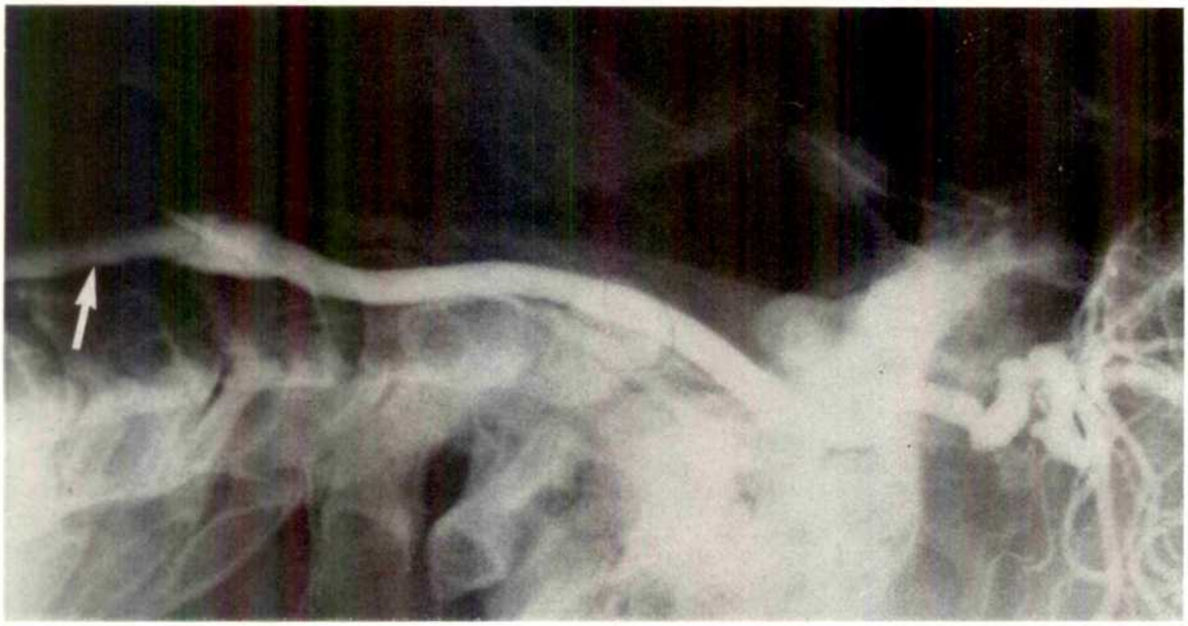

FIG. 2B.

Contrast arteriogram in which a Sheldon cannula was inadvertently placed directly into the internal carotid artery. The plaque shown in 2A was noticed retrospectively as a double density in the lateral decubitus film (arrow, 2B) in the retrogradely contrast filled common carotid but not in the antero-posterior view (2C).

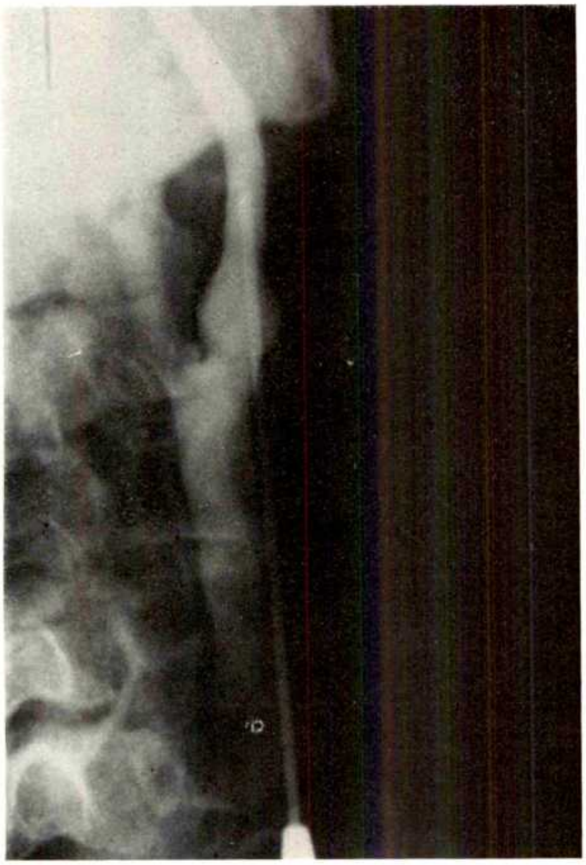

Fig. 2c.

6 mm probe attached to a standard commercial ultrasound apparatus* was passed lightly over the skin along the anticipated course of the artery, usually just medial to the margin of the sternomastoid muscle. Scans were repeated until maximum demonstration of the whole length of the artery was obtained, by altering the direction and angle of the scan if necessary. Excessively heavy pressure on scanning displaced the carotid artery to either side of the transducer making imaging of the artery unsatisfactory. However, in the more obese neck, penetration with a high frequency probe is too limited if pressure is not applied. In these cases, the artery was fixed with the non-scanning fingers between which the 6 mm diameter probe head was passed. The principle of this technique is similar to that applied when a Sheldon cannula is passed into the carotid artery for direct (X-ray) carotid arteriography. A stenosis shown longitudinally was confirmed when possible with transverse sections, first over the common carotid artery and then as serial scans moving in a cephalid direction. The rounded lumen of the common carotid artery could be seen to divide into the two smaller diameter external and internal carotid arteries.

Arteries with a smooth, intimal lining and an echo-free (dark) lumen were considered to be normal (Fig. 1). Intimal irregularities and intraluminal filling defects of variable echogenicity were interpreted as atheromatous plaques. Only those abnormalities which could consistently be reproduced were considered to be significant on examination with ultrasound since reverberation may produce artefacts simulating plaques especially in the anterior wall of a relatively superficial artery (Fig. 6a). The antero-posterior diameter of the lumen at the site of the stenosis was measured and an assessment of narrowing expressed as a percentage determined from the ratio between stenosis measurement and the maximum diameter of the normal section of the carotid artery. Ultrasonic assessment was completed in each case before the results of arteriography were available.

Transfemoral arch aortography with bilateral selective carotid artery catheterization was performed in seven of the nine patients. However, in one of these patients, the left carotid artery could not be catheterized and the examination was completed with a left direct carotid arteriogram (Case V, Table I). In two cases catheterization of the femoral artery was not possible and a direct unilateral carotid arteriogram was therefore performed (Cases I and III, Table I). In all cases, antero-posterior and lateral decubitus views of the carotid arteries were obtained.

Results

In three of the nine patients examined, all six carotid arteries, their bifurcations and internal and external branches were normal by both ultrasound (Fig. 1) and contrast arteriography. In the remaining six patients, ten common carotid arteries were studied by arteriography (Table I). Ultrasound demonstrated atheroma in five: stenosis in one (Fig. 3a.); atheromatous plaques in two (Figs. 2a and 3b); irregular anterior wall in one (Fig. 6a), and involvement of the distal anterior and posterior wall as a dense (echogenic) thickened area (Fig. 8a) adjacent to an 80% stenosis of the internal carotid artery in one.

In only two common carotid arteries were these findings confirmed by arteriography. A double density in the common carotid (Fig. 2b) was noted in one retrospectively. This was probably obscured

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*EMI/NE Diasonograph 4200, P.R.F. 600.

TABLE I

Comparative findings in the six patients with carotid occlusive disease

Case		Common carotid (C)		Internal carotid (I)		External carotid (E)	
		Ultrasound (Fig.)	X-ray (Fig.)	Ultrasound (Fig.)	X-ray (Fig.)	Ultrasound (Fig.)	X-ray (Fig.)
I	L.	Atheroma (2a)	*Carotid Artm.* Double density (2b)	Normal	Normal	Normal	Normal
II	L.	45% stenosis (3a)	*Arch Aortogram* Normal	66% stenosis (4c)	66% stenosis (4b) (4d)	66% stenosis (4a)	66% stenosis (4b)
	R.	Normal	Normal	Endarterectomy	Endarterectomy	Endarterectomy	Endarterectomy
III	L.	Irregular (6a) anterior wall	*Carotid Artm.* Irregular (6b) anterior wall	Normal (6a)	25% stenosis (6b)	stenosis (6a)	33% stenosis (6b)
IV	L.	Anterior plaque (3b)	*Arch Aortogram* Anterior plaque	Normal	Normal	Normal	Normal
	R.	Normal	Normal	Normal	Normal	Normal	Normal
V	L.	Normal	*Arch+L. Direct Carotid Artm.* Normal	Occluded (7a)	Occluded (7b)	50% stenosis (7a)	50% stenosis (7b)
	R.	Normal	Normal	20% stenosis	30% stenosis	< 10% stenosis	< 10% stenosis
VI	L.	Distal atheroma (8a)	*Arch Aortogram* Normal	80% stenosis (8a)	80% stenosis (8b)	Normal	15% stenosis (8c)
	R.	Normal	Normal	Normal	Normal	Normal	Normal

by a high direct carotid injection which was too distal to allow adequate demonstration of a proximal lesion. In another, the patient's shoulders precluded demonstration of the atheroma on a lateral decubitus examination. The proximal extension of the bifurcation atheroma was obscured by contrast on arteriography in the third case (Fig. 8C).

Internal carotid artery stenosis was demonstrated in four arteries by ultrasound and in five by arteriography (Table I). Stenosis, when present, ranged from 20% to total occlusion (Figs. 4, 6, 7 and 8).

Four external carotid arteries were shown by ultrasound to have a stenosis ranging from less than 10% to 66%. In one of these, a dense plaque of atheroma at the origin of the external carotid was demonstrated by ultrasound (Fig. 6A) but the extent of the atheroma was not anticipated by arteriography (Fig. 6B). Arteriography demonstrated one 15% external carotid artery stenosis (Fig. 8C) which was not detected by ultrasound. Where stenosis was present on contrast arteriography, ultrasound showed additional laminated plaques of atheroma in two (Figs. 4C and 8A) and thick echogenic walls in three (Figs. 4C, 7A, and 8A). In the two patients (Figs. 4 and 8) who underwent endarterectomy, the extent and nature of the atheroma was considered by the surgeon to be more accurately shown by ultrasound than by arteriography. In one patient, six months after undergoing endarterectomy, the absence of any atheroma in a non-stenosed artery is illustrated in Fig. 5.

Discussion

In a random series of 93 autopsies, Schartz and Mitchell (1961) showed that atheroma of the carotid and vertebral arterial systems occurred most frequently in the carotid sinus where it may be calcified. Stenosis, however, although most common in the vertebral arteries, was often present in the carotid sinus and common arteries.

Satisfactory demonstration of common carotid artery atheroma may be important since stenosis and/or plaques in this artery might impair the expected improvement in cerebral blood flow following endarterectomy or act as a secondary focus for emboli. The relatively non-tortuous and

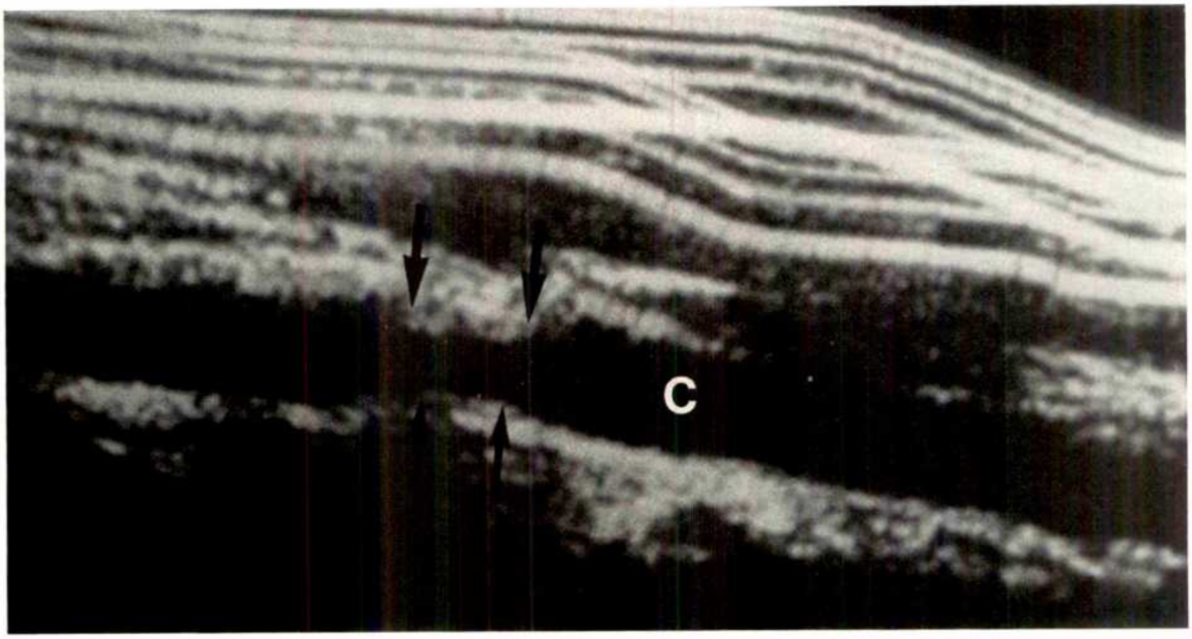

FIG. 3A.

Longitudinal section of a common carotid artery with a 45% stenosis which was not detected by contrast arteriography.

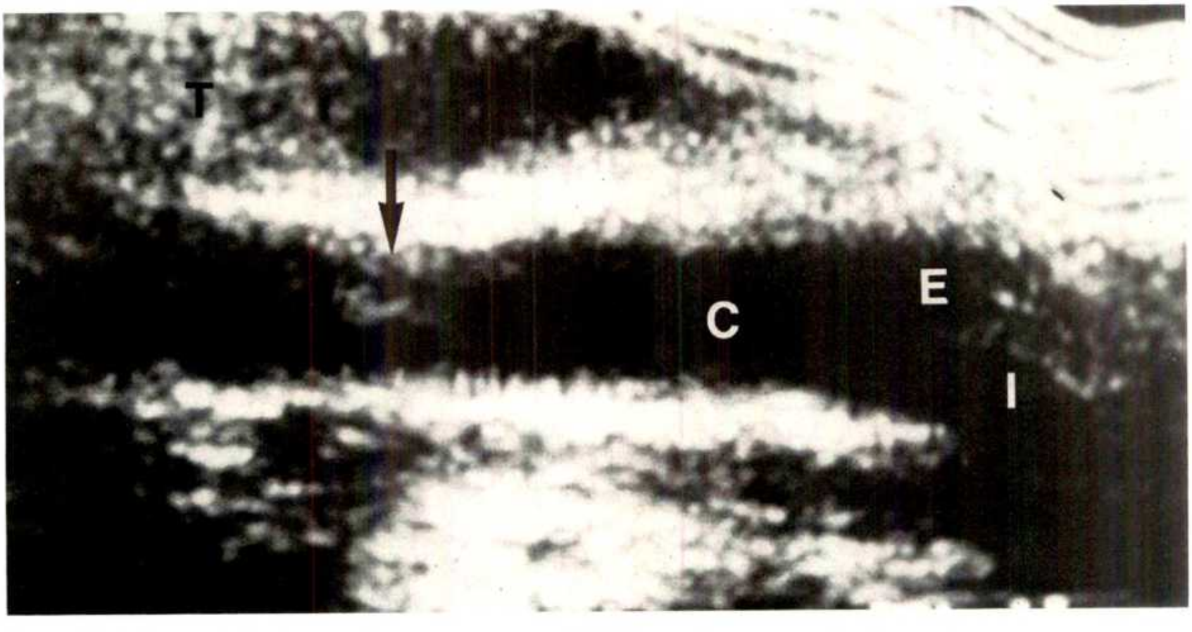

FIG. 3B.

Atheromatous plaque (arrowed) arising from the anterior wall of a common carotid artery and producing a 60% stenosis. This stenosis was also demonstrated by arteriography. The bifurcation is normal. C = common carotid artery, E = external carotid artery, I = internal carotid artery, T = thyroid gland.

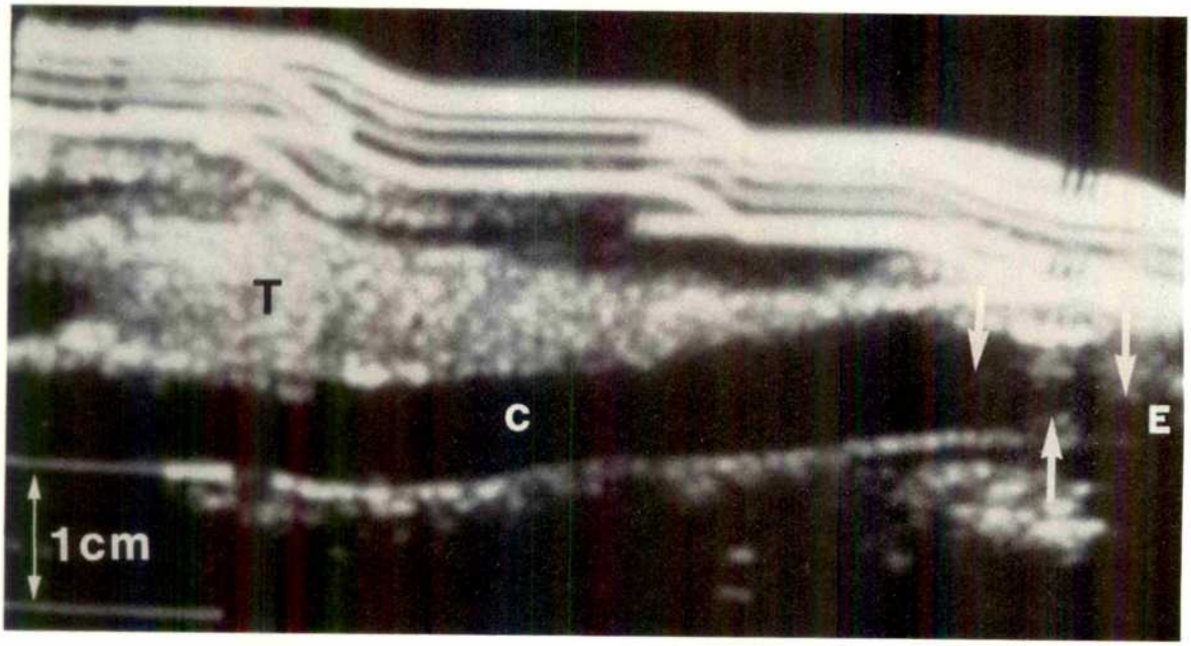

Fig. 4a.

Sagittal section of normal common carotid artery with the thyroid gland lying anteriorly. At the origin of the external carotid, there is a 66% encroachment of the lumen by rough atheromatous plaques (arrowed).
C = common carotid artery, E = external carotid artery, I = internal carotid artery, T = thyroid gland.

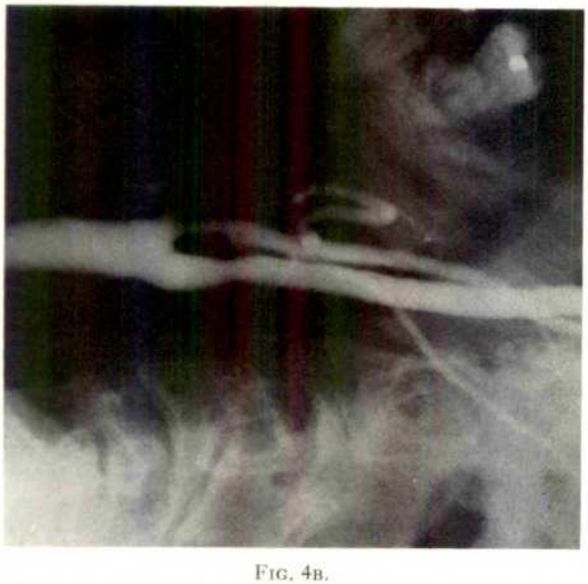

Fig. 4b.

Lateral decubitus contrast radiograph in which the external carotid artery rough plaque arrowed in Fig. 4a is shown arteriographically as a smooth walled 66% stenosis.

superficial course of the common carotid artery and bifurcation vessels permits high frequency contact grey scale scanning of these arteries in most patients. A normal thyroid gland provides a window through which the proximal part of the common carotid may be scanned. High resolution thyroid images can also be obtained by this method.

Common carotid atheroma may be obscured by contrast in an arteriogram in the frontal view and by the patient's shoulders in the horizontal beam lateral decubitus view. A low carotid bifurcation is more readily shown by ultrasound and a high bifurcation is better demonstrated by arteriography. Hence, arteries most easily shown by ultrasound happen, fortunately, to be those most accessible to surgery. In addition, if a direct carotid arteriogram is performed in the presence of a low bifurcation, there is a greater probability of inserting the needle directly into either the external or internal carotid arteries (Figs. 2b and c). This precludes a satisfactory angiographic assessment of the common carotid unless the needle is resited, and is more

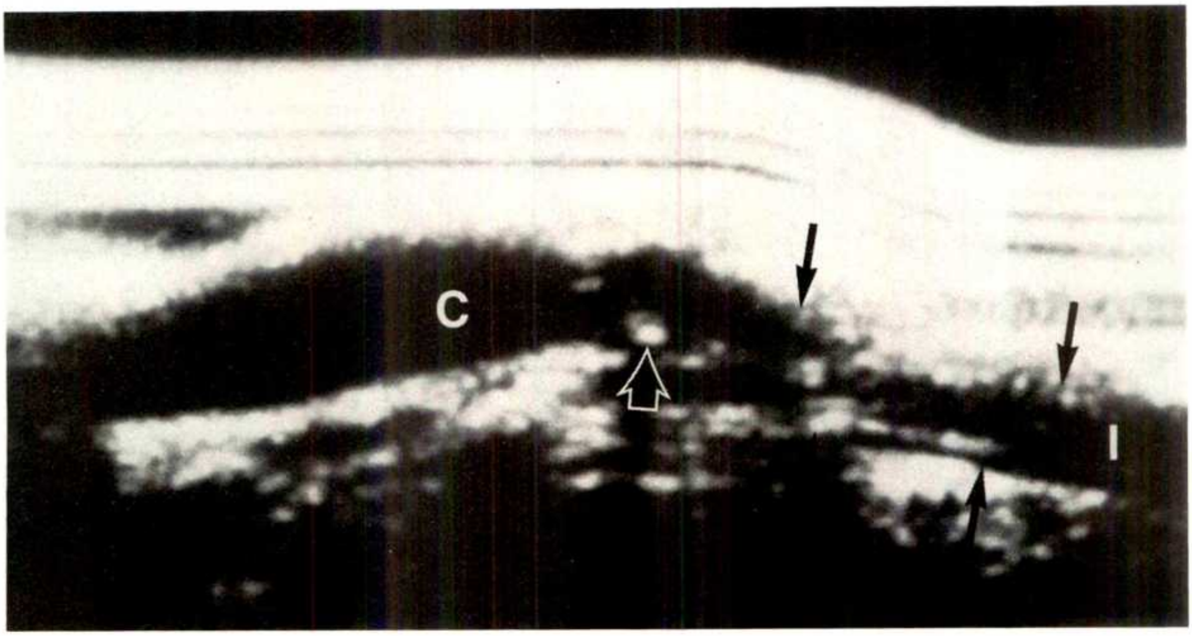

FIG. 4C.

Same patient as in Fig. 4A, but the longitudinal section is more laterally placed to demonstrate the internal carotid artery. There is a 1.5 cm long 66% stenosis (between black arrows). The atheroma appeared laminated on the posterior wall of the stenosis. Open white arrow indicates extension of atheroma to the bifurcation not demonstrated in either Fig. 4B and 4D.

likely to occur in the shorter neck of an obese patient.

The internal carotid artery was more readily demonstrated by ultrasound than the external carotid artery since the former tends to lie in the same longitudinal plane as the common carotid artery. Generally, the internal carotid assumes a posterior deflection at the level of the bifurcation (Figs. 2A, 4C, and 6A).

Gomensoro *et al.* (1973), in a retrospective study, noted that there was a good correlation of radiographic findings with those of surgery when the lesions were far advanced or roughened, but poor correlation when smooth or minimal. These authors further noted that rough atheroma occurred in a significantly greater number of patients with stenosis more than 50%. Similarly, the presence of rough atheroma in a 66% smooth arteriographic stenosis (Figs. 4B and D) has been demonstrated by ultrasound (Figs. 4A and C) in this series. In an attempt to improve the accuracy of arteriography, Hugh (1970) suggested trickling concentrated contrast into the artery. Using a horizontal X-ray beam, he demonstrated pooling of contrast in the

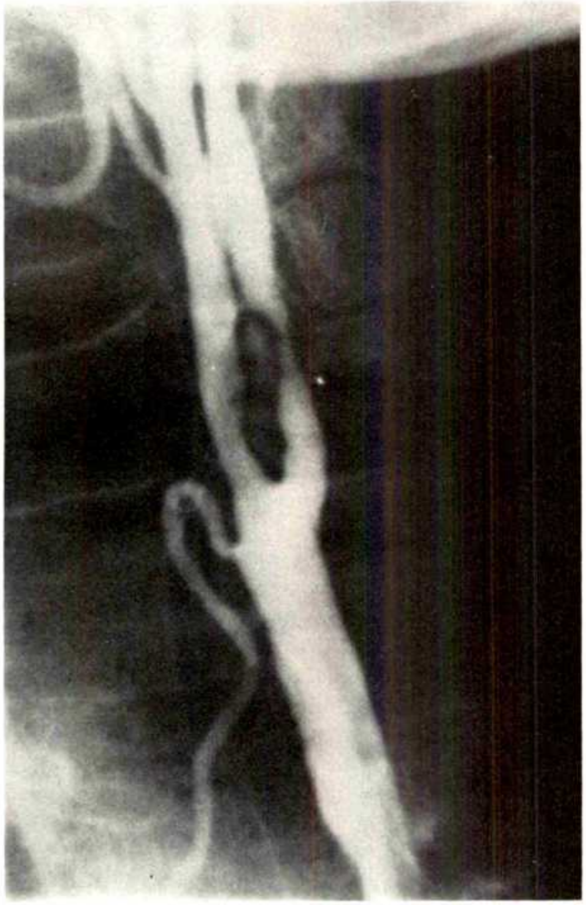

FIG. 4D.

Antero-posterior view of selective carotid arteriogram which, in this case, demonstrated the internal carotid 66% stenosis more clearly than the lateral decubitus view of 4B.

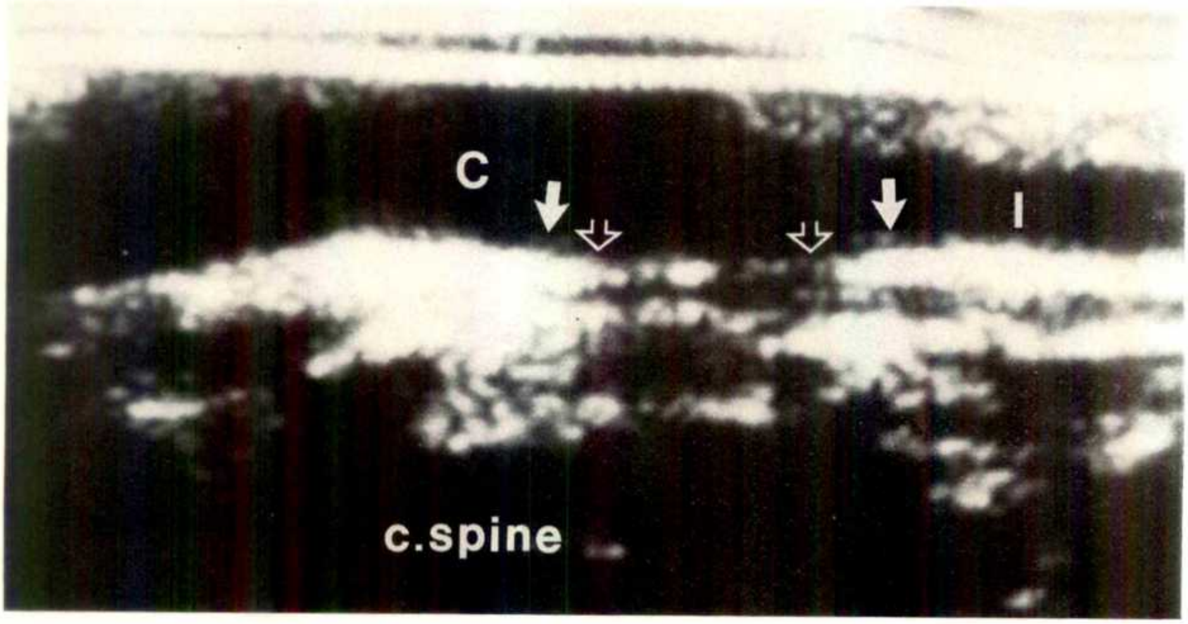

Fig. 5.

Sagittal section of post-endarterectomy bifurcation. No atheroma filling defects are present. The arterial wall, although smooth, is of variable thickness due to the endarterectomy. Black arrows show normal external carotid artery wall, open arrows indicate thinned post-endarterectomy wall.
C = common carotid artery, I = internal carotid artery.

posterior carotid wall ulcerations and an improvement in identification of intra-luminal thrombus.

As in this series, Mercier *et al.* (1978), and Green (1978) found a closer correlation between surgical findings and appearances of atheromatous plaques in the common and internal carotid arteries demonstrated ultrasonically than with those shown by arteriography.

For Lota and Sherrad (1971), stenosis appeared more severe with ultrasound than with arteriography although the degree of stenosis was similar by both methods in the series of cases now being reported. The ability of ultrasound to differentiate a high grade stenosis from total occlusion has been questioned (Mercier *et al.*, 1978) but it is noted that in the present series an occluded internal carotid was reliably demonstrated.

Atik *et al.* (1973) suggest that a critical degree of stenosis resulting in a significant reduction in blood flow depends upon a number of factors such as diameter, length and rigidity of the vessel, the length of the stenotic segment, viscosity of the blood, and the status of the collateral circulation. Other factors such as intra-arterial thrombus and small atheromatous ulcers may be the source of platelet aggregates (McBrien *et al.*, 1963) and cholesterol emboli (Russell, 1965) and so produce transient ischaemic attacks. The ability of ultrasound to give accurate information about many of these factors gives ultrasound an important role in the evaluation of the signs of cerebral ischaemia and their aetiology. A larger series with further correlation with surgical and arteriographic findings will be necessary to reassess the reliability of ultrasound in this context.

A bilateral carotid ultrasound examination takes 15–30 minutes to perform and is a safe and cost-effective investigation. It should be capable of preselecting those cases which would benefit from contrast arteriography and therefore prevent the performance of a potentially hazardous procedure in the presence of normal arteries.

Conclusion

High frequency grey scale ultrasound reliably outlines the extent and severity of atheromatous plaques and stenosis in the common carotid artery and its bifurcation vessels. It is suggested that it may be used as an initial non-invasive method to preselect those patients suitable for contrast arteriography. Information provided by ultrasound generally more accurately coincides with surgical

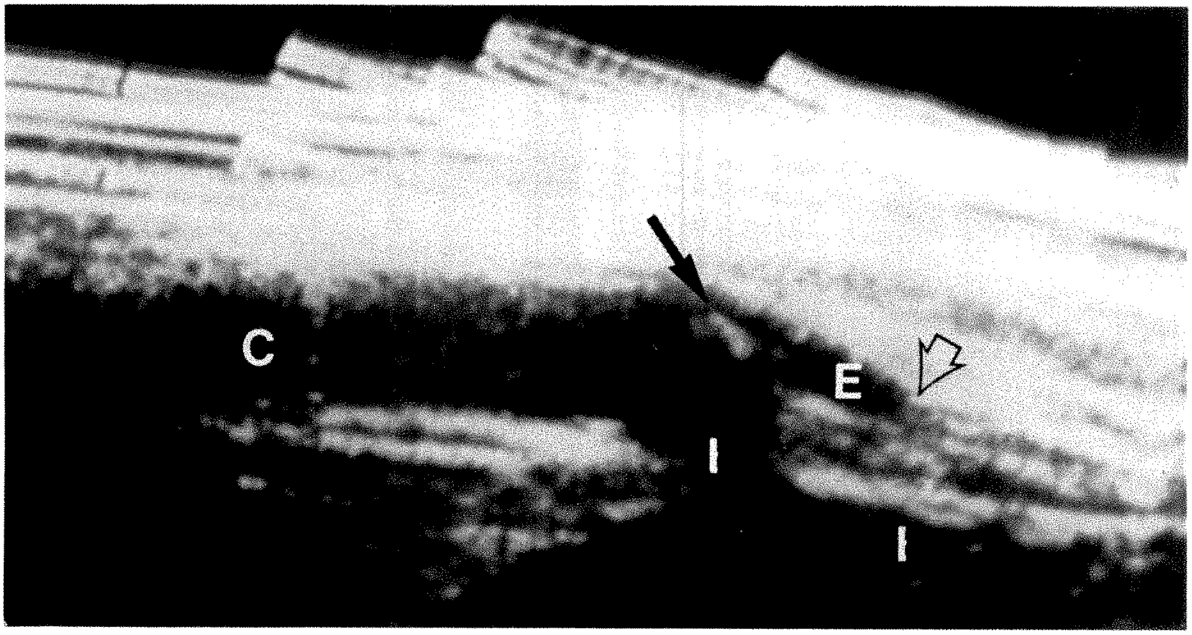

Fig. 6a.

Longitudinal section of carotid bifurcation demonstrating an atheromatous plaque (black arrow) almost occluding the origin of the external carotid artery. The open arrow indicates site of external carotid stenosis, just distal to the bifurcation. The anterior wall of the common carotid artery is ill-defined, largely due to reverberation. However, atheroma of the anterior wall was demonstrated in the lateral decubitus arteriogram (Fig. 6b).
C = common carotid artery, E = external carotid artery, I = internal carotid artery.

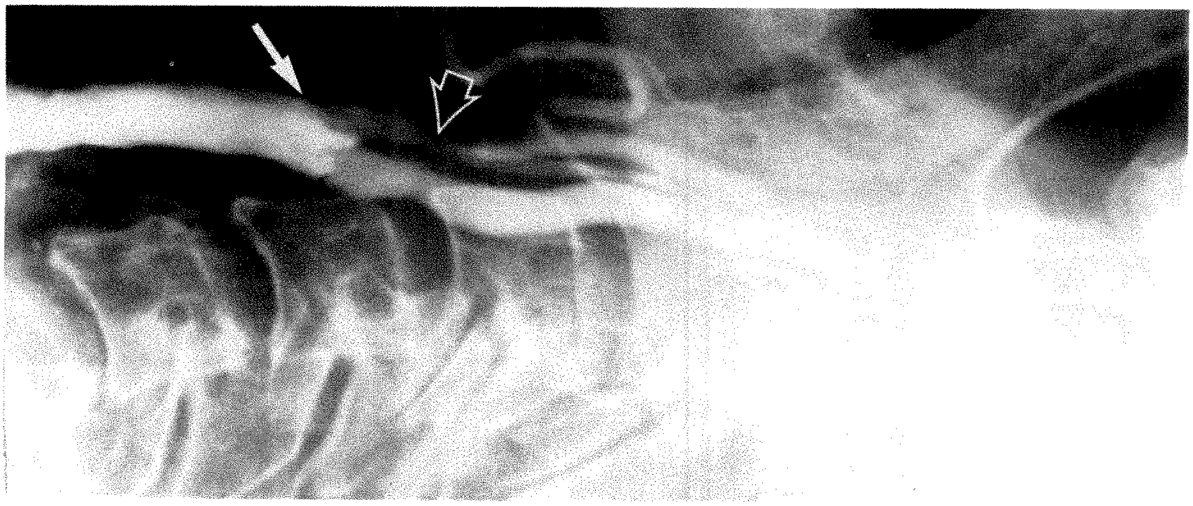

Fig. 6b.

Lateral decubitus view of carotid bifurcation. The white arrow points to a double density of contrast which correlates with the position of the atheroma shown in Fig. 6a. The open arrow indicates the external carotid 33% stenosis.

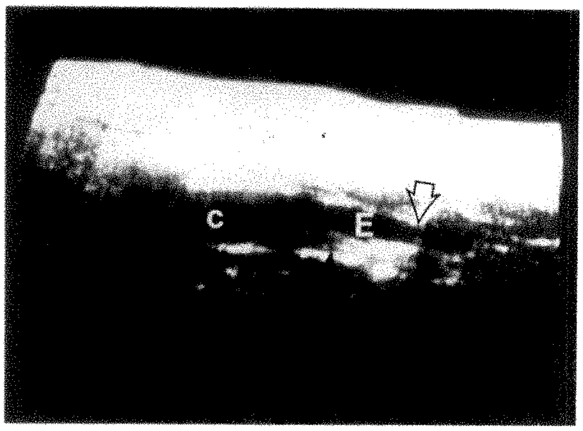

Fig. 7A.

Longitudinal ultrasound scan of common carotid and external carotid arteries demonstrating a 50% stenosis (open arrow). The black arrow indicates atheroma projecting into the lumen of the bifurcation and which is occluding the internal carotid artery.
C = common carotid artery, E = external carotid artery.

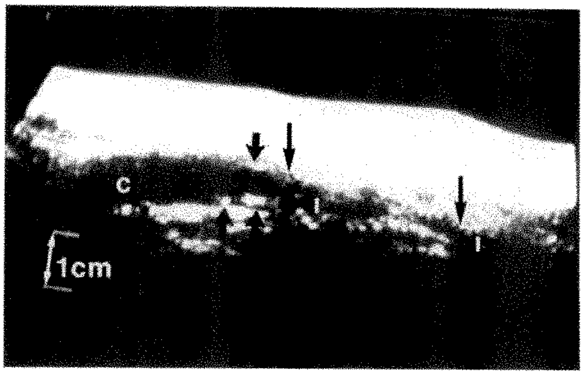

Fig. 8A.

A 3.5 cm long 80% stenosis of the internal carotid artery (between long black arrows). The dense, echogenic arterial wall at the stenosis appears laminated and irregular. Atheroma extends a further centimetre into the bifurcation (short black arrows).

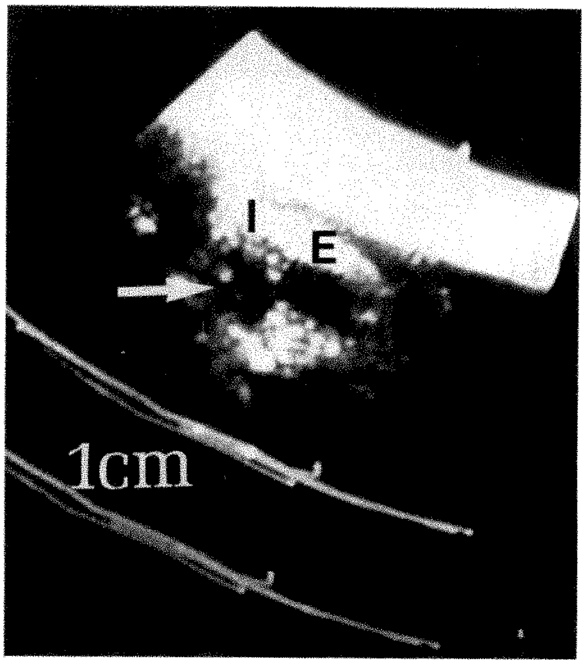

Fig. 8B.

Transverse section of internal and external carotid arteries just distal to the bifurcation. Atheroma can be seen encroaching upon the lumen of the internal carotid artery (arrowed).
C = common carotid artery, E = external carotid artery, I = internal carotid artery.

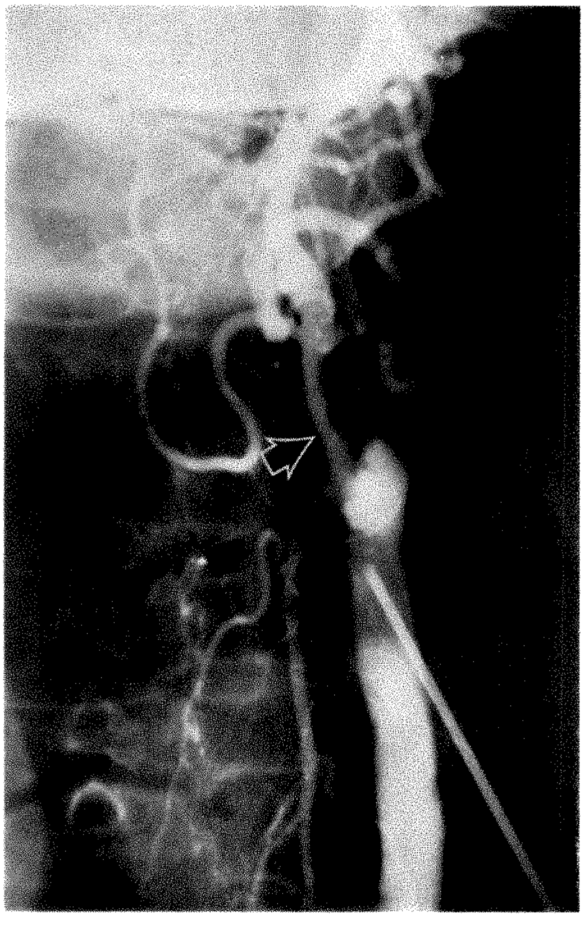

Fig. 7B.

Antero-posterior view of common carotid artery and bifurcation (direct common carotid puncture). The internal carotid artery is occluded. The open arrow indicates a 50% stenosis which correlates with the narrowing shown by the open arrow in Fig. 7A.

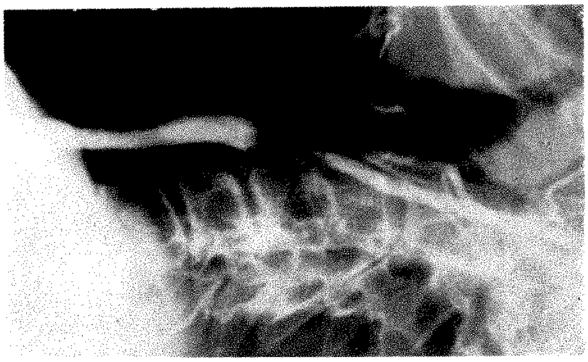

FIG. 8C.

Lateral decubitus view of carotid arteriogram. The 80% internal carotid stenosis appears to extend only 3 cm compared with a total of 4.5 cm on ultrasound (Fig. 8A.). The arrows point to calcified areas within the thickened posterior wall of the internal carotid artery. This is similar to the appearance of the posterior wall shown by ultrasound (Fig. 8A). There is also a 25% external carotid stenosis.

findings than details from arteriography but the latter has the advantage of displaying the distribution of atheromatous disease throughout the carotid and vertebral arterial systems. Ultrasound also should be of considerable value where there is known sensitivity to contrast media, for post-operative serial assessment, and to detect proximal common carotid lesions.

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Contrast dose for enhancement of computed tomograms of the brain

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ABSTRACT

This study shows that contrast enhancement of cerebral lesions can be adequately achieved with a bolus injection of 60 ml of sodium iothalamate 70%. While the infusion of a larger dose of contrast agent increases quantitatively the level of enhancement of a variety of lesions, this method of examination does not appear to provide any more useful diagnostic information, and it introduces added and unnecessary inconvenience, cost and potential hazard.

Intravenously administered radiological contrast agents have been shown since early experience to be useful adjuncts to computed tomography in the visualization of intracranial lesions (Ambrose, 1973; Paxton and Ambrose, 1974; New *et al.*, 1974). Large doses of contrast medium have been advocated in an attempt to demonstrate these lesions more effectively (Ethier *et al.*, 1974, Kramer *et al.*, 1975).

It is established that the plasma concentration of a contrast agent, in the initial few minutes after intravenous injection, is primarily a function of dose and body size (Cattell *et al.*, 1967). With this in mind an attempt was made to demonstrate the effect of varying the quantity of contrast medium used, as well as its rate of administration, upon the enhancement of various types of cerebral lesions, in order to determine if higher or more sustained circulating iodine concentrations increase the diagnostic yield.

MATERIAL AND METHODS

The established practice in the Wessex Neurological Centre, Southampton is to enhance computed tomographic scans of the brain in adults with 60 ml of sodium iothalamate 70% (Conray 420), given as a rapid intravenous injection. The scans are then made directly, as soon as the patient has recovered from the effects of the injection. To challenge the adequacy of this method a series of 20 patients was recalled within 72 hours of their initial examinations and their scans were repeated. Upon recall the patients were separated into two groups, namely those given a continuous infusion of 60 ml ("small dose group"), or those receiving 120 ml of sodium iothalamate 70% by infusion ("large dose group").

The patients were selected to provide a representative mixture of commonly encountered cerebral lesions, the diagnosis in each being substantiated histologically or otherwise. One patient, a case of cerebral abscess which required multiple scans to assess progress, is included in both these groups.

The examinations were performed on an EMI CT 1010 head scanner using a 160 × 160 matrix. The procedure was carried out at 120 kV with a scanning time of 80 seconds per slice. It will be noted that the new series of Hounsfield units are employed on this equipment.

The initial examination in each patient consisted of unenhanced and enhanced slices, the enhanced examination always commencing within five minutes of the injection and taking approximately ten minutes to complete. After studying recent publications concerning contrast enhancement with respect to the time after injection (Hatam *et al.*, 1975; Sato *et al.*, 1976) the practice was established to recommence scanning about five minutes after the contrast injection, because all lesions show a satisfactory although perhaps not optimal degree of enhancement at this time.

In the repeat examination a continuous infusion was set up with either 60 ml or 120 ml of sodium iothalamate 70% diluted with an equal volume of normal saline. The infusion was started 15 minutes before scanning commenced and three-quarters of the volume was administered in this initial period, and the remainder during scanning.

In each case the examination was carried out with the informed consent of the patient; the study as a whole having been approved by the local Ethics Committee.

In order to validate the clinical method, venous blood samples were obtained before the examination, and also after contrast injection at the start and finish of scanning. Experimentally, it was possible by scanning serial dilutions of sodium iothalamate 70% to verify the linear relationship between the iodine concentration of a solution and its attenuation value, as reported by Riding *et al.* (1975) and Gado *et al.* (1975). An increase in iodine concentration of 1 mg per ml will raise the attenuation coefficient by approximately 26 Hounsfield units. The iodine levels obtained in the patients' blood could then be established by scanning the blood samples in a phantom, and subtracting the pre-contrast attenuation values from the post-contrast.

A quantitative estimate of the enhancement of the pathological lesions was then made by deducting the attenuation value of the corresponding area on the unenhanced scan from the attenuation value of the enhanced lesion. A direct comparison of the degree of enhancement obtained by the two methods of contrast enhancement was then possible.

Results

Table I lists the results in the 20 patients. The enhancement obtained by the bolus and infusion methods are compared in both the large and small dose groups.

In the large-dose group all of the lesions which had enhanced with the 60 ml contrast bolus showed a greater rise in attenuation coefficient with infusion. The two lesions which failed initially to enhance, namely a small arteriovenous malformation and a subdural haematoma, failed also to enhance with infusion. All of the lesions in the small-dose group enhanced with both examinations; but of these five showed a greater rise in attenuation with the bolus injection, three greater with the infusion, and in two the degree of enhancement was considered to be the same in each patient.

TABLE I

Comparison of the contrast enhancement between bolus and infusion methods, using Hounsfield units, in each of the 20 patients

Patient No.	*Large dose* *Pathology*	*Bolus*	*Infusion*
1	Astrocytoma	5	10
2	Astrocytoma	13	15
3	Pituitary adenoma	10	23
4	Metastasis	23	30
5	Metastasis	15	22
6	Subdural haematoma (isodense)	0	0
7	Pyogenic abscess	15	25
8	Pyogenic abscess	21	30
9	Arteriovenous malformation (frontal)	0	0
10	Arteriovenous malformation (temporal)	9	20
11	Arteriovenous malformation (parietal)	32	43
	Small dose		
12	Glioblastoma	10	9
13	Astrocytoma	20	22
14	Astrocytoma	20	15
15	Oligodendroglioma	5	5
16	Sphenoid meningioma	35	37
17	Metastasis	14	13
18	Metastasis	9	11
19	Acoustic neuroma	24	22
20	Cerebral infarct	5	5
8	Pyogenic abscess	21	20

The circulating iodine levels recorded during the course of the bolus and infusion examinations for one patient in each group are set out Fig. 1. Each is representative of its group, so that for the sake of simplicity only these two examples have been depicted. Figure 1 demonstrates that in the patients of the small-dose group the iodine level in the blood at the start of the examination was lower with the infusion than with the bolus method. However, the blood level is more sustained with infusion, so that by the end of the examination the blood level of iodine was approaching or had surpassed that with the bolus. In the large-dose group the initial blood level present during infusion equalled or was higher than that following bolus injection, but the sustained level obtained by infusion further increased this difference before the end of scanning.

Discussion

The term contrast enhancement of a lesion expresses the increased amount by which that lesion will further attenuate the X-ray beam after contrast medium is introduced into the circulation. A lesion enhances relative to the surrounding brain tissue because injected contrast medium accumulates preferentially within it. This enhancement is believed to

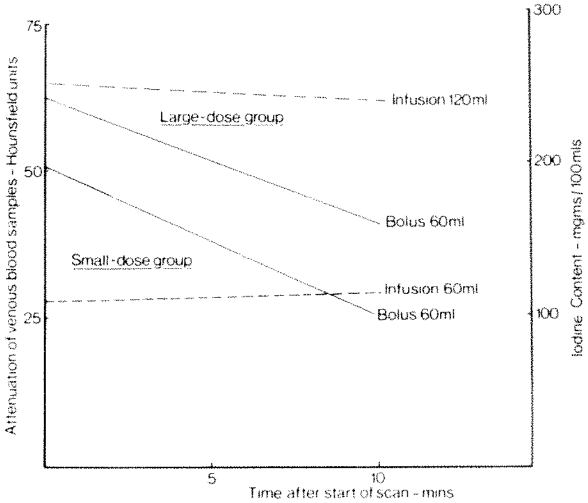

Fig. 1.

Circulating level of iodine in one patient from each group after injection of contrast medium.

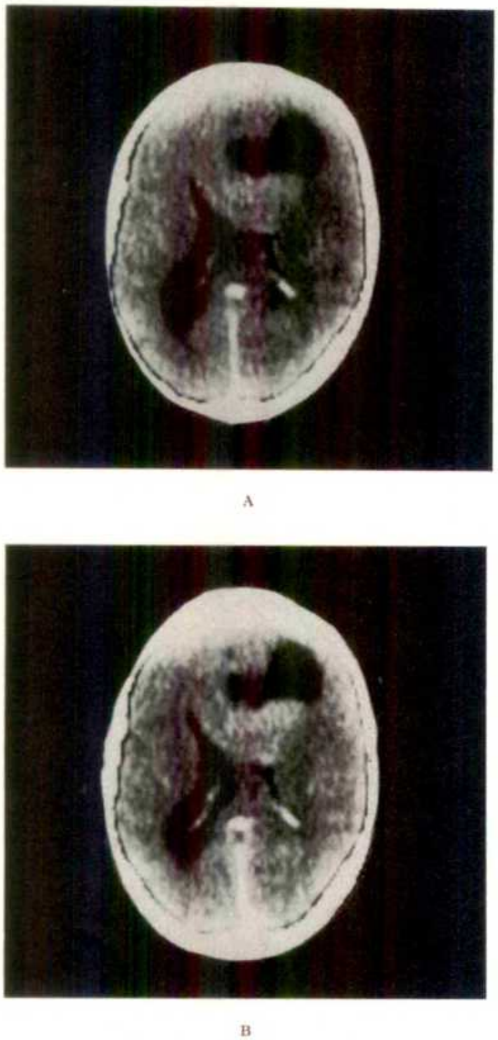

FIG. 2.

Glioma of the corpus callosum as shown by enhanced computed tomography.
(A) Small-dose bolus.
(B) Large-dose infusion.

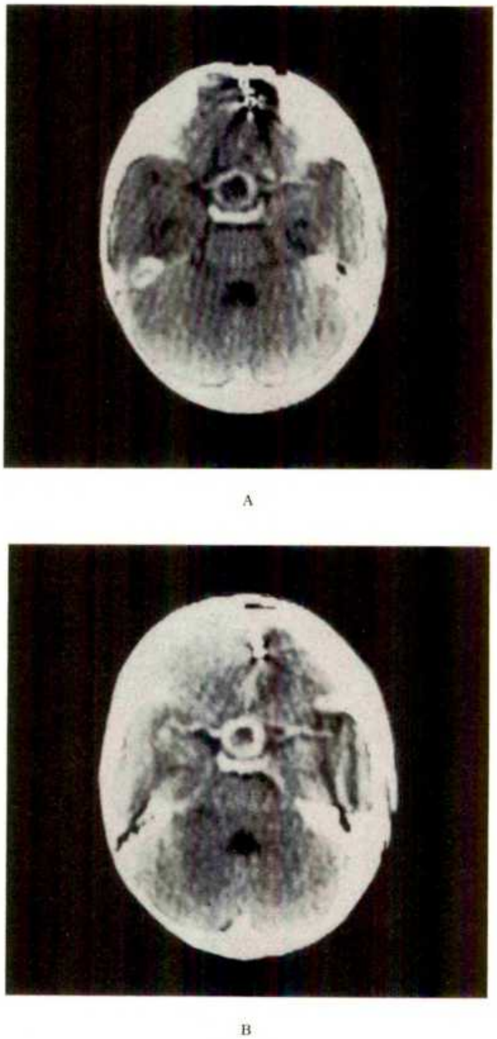

FIG. 3.

Pituitary adenoma visualized by enhanced computed tomography.
(A) Small-dose bolus.
(B) Large-dose bolus.

depend upon a combination of intra-vascular and extra-vascular contrast medium (Gado *et al.*, 1975) and it might reasonably be expected that a higher plasma iodine concentration would produce greater enhancements. The results of this investigation bear this out, in concordance with the work of Ethier and others.

Large dose group

The important findings were that a large dose of contrast medium administered by infusion resulted in a higher and more sustained level of circulating iodine. Using this method, various individual lesions were shown to demonstrate greater enhancement than with a small dose injected as a bolus. Figures 2 and 3 are representative samples. However, the radiologists' concern in the department is to achieve adequate contrast enhancement, and in this study no further diagnostic information was obtained with a large dose.

Small dose group

Introduction of the same dose of contrast medium by continuous infusion did not improve the level of enhancement over that achieved by bolus injection in any of the ten patients examined by this method.

Not only did the infusion scan fail to offer positive advantages in these patients, but there are several disadvantages associated with its use. The intravenous drip requires setting up by a doctor and observation by the nursing staff, and it introduces additional scheduling problems, all of which are inconvenient in a busy X-ray department. There is a small added cost to the examination of the extra contrast medium and other consumables; but more important is the increase in the risk of potentially hazardous side-effects to the patient. Although the large dose of contrast medium may not increase the risk of serious allergic reactions, it may dangerously overload the circulation in the elderly patient to produce congestive heart failure (Davies *et al.*, 1975). With this in mind, care was taken in the selection of patients for inclusion in this study.

ACKNOWLEDGMENTS

Thanks are due to the consultant staff of the Wessex Neurological Centre for permitting their patients to be included in this study, and to Dr. E. H. Burrows for his help in preparing this paper.

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Book review

Radiologic Management of the Massively Traumatised Patient. by R. J. Ayella (with contributions by J. N. Diaconis, M. B. Isikoff, C. E. Nagle, J. W. Ryan and G. S. Johnson), pp. xv+297, illust., 1978 (Baltimore, Maryland, Williams and Wilkins Company), $40.
ISBN 0-683-00296-1

Patients with major injuries constitute an important clinical entity presenting serious problems in management. The degree of urgency precludes the development of a diagnostic approach at the time of presentation. A text book entirely devoted to this topic is therefore most welcome. It consists of two introductory chapters, followed by 11 which deal with regions and body systems. The subjects of CT head scanning, ultrasound and radionuclides have not been incorporated in the regional discussions and are discussed in separate chapters.

The script is succinct and presents the wide experience of the author in a style which is easy both to read and to assimilate. The book is well produced with high quality illustrations particularly when the clinical difficulty surrounding the original production is considered. There is a good index and there are ample well selected references. The author emphasizes the importance of a clear diagnostic protocol starting with the lateral view of the cervical spine to be taken as soon as the patient's condition permits. Unfortunately the chapter dealing with the cervical spine follows three concerning the head and face which may lead to some confusion in the mind of the reader.

Not all the recommended approaches will meet with universal support in this country. For example there is no mention of the invaluable supine posterior oblique views of the cervical spine. The single shot carotid arteriogram will be considered by many to be an unnecessary abbreviation of this investigation. The author also recommends a rather aggressive investigation style in the management of renal trauma.

There are invaluable lessons to be learned from this book and the discussion it will certainly stimulate can do nothing but good. It can be recommended for inclusion in the libraries of departments of accident and emergency and of radiodiagnosis, providing a concise collection of relevant data which will stimulate thought before an acute emergency presents.

John Roylance.

1979, *British Journal of Radiology*, *52*, 624–625

Fetal hydrocele detected *in utero* by ultrasound

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ABSTRACT

Demonstration of the fetal detail *in utero* has been more refined with advances in equipment and technical skill. Abdominal and genital abnormalities are being increasingly described. Presented are two cases of hydrocele diagnosed *in utero*.

Original demonstration of fetal detail by ultrasound was confined to gross neural abnormalities such as anencephaly and hydrocephalus. With refinement of equipment and increased technical expertise, abdominal and genital detail, both normal and pathological, has been described (Carroll, 1977; Lee and Blake, 1977; Lee and Warren, 1977; Schorzman, 1977; McQuown *et al.*, 1975). Since hydroceles are not uncommon findings at birth and genitalia are being recognized more frequently, one would expect *in utero* diagnosis of hydroceles.

Recently, two cases of bilateral fetal hydroceles were seen in our department as incidental findings. The patients had been referred for fetal dating. A unilateral hydrocele has been previously reported associated with fetal hydrops, pulmonary hypoplasia, and pleural effusions (Carroll, 1977). No fetal abnormalities at birth were found in either of our patients. Bilateral hydroceles were confirmed in both patients.

CASE REPORTS

Case 1

A 23-year-old female was evaluated by ultrasound because of post-maturity. A single fetus with a biparietal diameter which correlated with a term gestation was demonstrated. Both testicles were descended in a large transonic scrotum. No other abnormalities were found at birth in this term infant.

Case 2

A 30-year-old female was evaluated with ultrasound on three occasions during her pregnancy. Examination at 11 and 32 weeks of gestation were unremarkable. The final examination was performed for post-maturity. A term gestation was diagnosed. Bilateral hydroceles were found and both testicles were descended. No other abnormalities were found at birth.

Transverse scans of the fetal abdomen are performed in the majority of our patients for cephalic–abdominal ratio determination. The genitalia, when seen, most often show attachment to the perineum. The hydroceles in these cases were so large that they appeared separate from the fetuses. This produced some initial uncertainty until testicles were found in the enlarged scrotum of the fetus.

Hydroceles may be communicating or non-communicating depending on the patency of the processus vaginalis. Most of the time, they are incidental findings at birth. Hydroceles have been seen by others as well as ourselves in adults. These are the first bilateral fetal hydroceles described in the ultrasound literature. The clinical significance of fetal hydroceles is usually only incidental. Recently an infected hydrocele (pyocele) which required

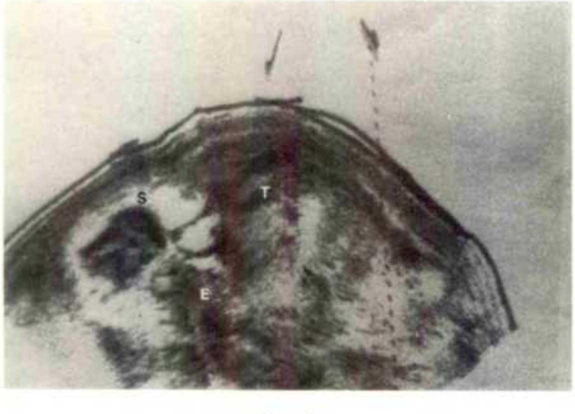

FIG. 1.

Transverse scan which shows the hydroceles (S) and their relationship to the trunk (T) and a lower extremity (E).

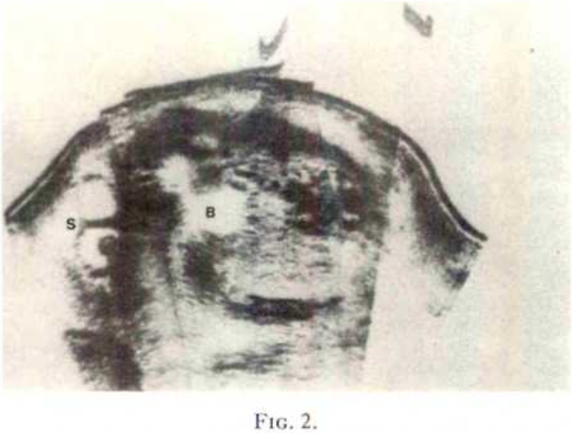

FIG. 2.

Longitudinal scan showing the bladder (B) and the hydroceles (S), and the apparent separation from the perineal tissues.

orchidectomy was described in a neonate (Jones and Deetes, 1975).

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Book review

Clinical Biostatistics. By Alvan R. Feinstein, pp. xii+468, 1977 (St. Louis, C. V. Mosby Co.) Paperback £10·75.

Most doctors read and many write,
It thus becomes essential quite
That all acquire some sort of knowledge
About statistics at their college,
Lest later on their publications
Give rise to muttered imprecations.

Professor Feinstein in this book
Has had a long and careful look
At methods used by statisticians
To aid (maybe confuse) clinicians.
But do not think the cunning Prof.
Does nothing more than sneer and scoff:
He shows how two and two make four—
Or if they don't, how to explore
The reasons for this grave omission—
A subject for great erudition.

Based upon lectures though this text
Is repetitious; one is vexed
By turgid prose and places too
Where fewer words would really do.
There's no remission to enchant
From diagrams or tables scant.
Despite these drawbacks some would gain
To read right through, and yet again
Some part could well be read by all
With benefit beyond recall.

Read by the sturdy devotee
Some simple truths emerge, *e.g.*,
"Like only with like should compare"
(Yet some *are* more alike I swear):
"Patients choose doctors"—the reverse
But seldom happens—that's the curse
That from a morbid population
The "rancid sample" has causation.

"Statistical procedures never
Prove anything"—but by a clever
Manipulation of your data
Show that the risk of chance is greater
Than the result you hoped to show
(And then they say—"I told you so!")
So we are warned the reasons why
One should beware the square of chi.

Full chapters look at the design
Of therapeutic trials, and shine
Some light on diagnostic tests
To show just where their value rests.
Controls and bias are displayed,
With cautions too on studies made
On past and future generations
And why we use stratifications.
All these and other points reveal
How to advance the common weal.

A minor pearl of wit I found
And trials clinical expound—
"An exercise where a clinician
With methods from a statistician
(Which doctors don't quite understand)
He draws conclusions that must stand
From data that are still unclear
To statisticians far and near."
And if the answers be expressed
In SI units—all is blessed
By Editors. Alas, that we
Such suckers simple seem to be!

The print is clear and well provided
With indices which are divided
For authors, methods, and examples
To help you get those "random samples".

Godfrey Price.

1979, *British Journal of Radiology*, *52*, 626–633

A quantitative evaluation of film and film/screen combinations for mammographic examination

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(*Received March 1978 and in revised form January 1979*)

ABSTRACT

A test phantom containing simulated micro-calcifications was constructed. This was imaged by seven systems suitable for use in mammography, firstly in scatter-free conditions and secondly with the addition of tissue-equivalent scattering material. The ability of the systems to resolve micro-particles of known size was assessed using the techniques of signal detection theory. The resultant receiver operating characteristic curves separated the systems into three major groups. Firstly, high resolution systems requiring high radiation dose techniques; secondly at the other extreme, a mediocre imaging system producing its results at low radiation levels; and thirdly a larger middle group producing intermediate resolution of fine particles at similar, acceptable dose levels. The ability to image small particles does not increase linearly with the radiation dose. Scatter did not affect all of the systems to the same extent.

The South Manchester Breast Clinic was one of several centres requested by the DHSS to investigate the feasibility of providing a breast cancer screening service for well-women. One of the principal questions to be answered concerned the levels of radiation dosage in mammography. In an earlier paper (Asbury and Barker, 1975) the radiation dose levels to the skin of the breast were recorded for industrial film and for several film-screen combinations. It was concluded that several of the film/screen systems were acceptable, in respect of radiation dosage, for use in screening programmes and that they complied with the upper limit of total radiation dose of 2 rad previously recommended by Ellis (1972). Since that time many new film-screen combinations have been developed for use in mammography, and this paper details a method of recording their image quality in relation to radiation dose.

This method makes use of signal detection theory which has previously been applied to the assessment of radiographic imaging systems (Goodenough *et al.*, 1972, 1973, 1974; Goodenough 1975). This technique has the particular advantage of giving due emphasis to the subjective factors which are an integral component of the diagnostic process. Other physical parameters such as the modulation transfer function and the Weiner spectrum of radiographic noise do not make any such allowance for this aspect of radiographic performance.

Visual detection experiments employing a test phantom have been performed and the results used to generate receiver operating characteristic curves (ROCs). The particular criterion of image quality simulated by this test object was the presence or absence of micro-particles. These have been imaged both with and without the addition of tissue-equivalent scattering material.

MATERIALS AND METHODS

Phantom design

Six test phantoms were constructed. Each consisted of a piece of Perspex measuring $10 \times 10 \times 0.5$ cm. These were divided into 100 squares of equal area by placing fine wire into grooves milled at 1 cm intervals parallel to the edges of the phantom. Small soda-glass beads were used to simulate the micro-calcifications commonly seen in breast carcinoma. These glass beads have the particular advantage of being perfectly regular in shape. Using phosphor bronze sieves of differing mesh size the glass beads were divided into six size groupings. Beads of a single size grouping were further graded by measuring their diameter with a vernier travelling microscope. The mean bead size used for each of the six phantoms is listed in Table I together with the standard deviation within each size group.

For each phantom 50 beads of one particular size grouping were distributed amongst the squares in a random fashion. Care was taken to ensure that there was no more than one bead per square and these were secured by means of adhesive tape. The

TABLE I

THE MEAN BEAD DIAMETERS EMPLOYED IN EACH OF THE SIX TEST PHANTOMS

Mean bead diameter (μm)	160	197	247	300	356	400
Standard deviation (μm)	6	14	15	8	8	7

position of the beads on each phantom was recorded for subsequent use in the analysis of the results.

Radiographic conditions and film/screen systems

The X-ray equipment used was a Watson Mammostand. This has a rotating molybdenum target with focal spot sizes of 2 mm and 0.8 mm. The inherent filtration of the tube was equivalent to 0.5 mm of aluminium and no added filtration was used. Radiographs of all the phantoms were produced for each imaging system both with and without the addition of 4 cm of tissue-equivalent scattering material placed on top of the phantom. This material was developed at St Bartholomew's Hospital (White, 1977).

The imaging systems tested are shown in Table II. The Kodak Industrex C film, a non-screen industrial film, was supplied in an individual light-tight envelope. The other film/screen combinations were vacuum packed to ensure maximum film-screen contact and at all times the screen was employed as a back screen. The systems listed in Table II contain examples of conventional calcium tungstate and both green and blue emitting rare-earth phosphor materials. The Kodak min-R, Trimax αM and α4 screens employ green emitting rare-earth phosphors. The Agfa-Gevaert MR50 screens use blue emitting rare-earth phosphors; the Ilford High Definition and Du Pont Lo-Dose screens are based on calcium tungstate.

All the systems were exposed at 30 kV tube potential and an FFD of 70 cm. The mAs value was selected for each system so that approximately unit density was achieved. The film densities were recorded using an EEL densitometer. Characteristic curves were produced for each film/screen combination to ensure that the operating density of one lay in the region of correct exposure for the detection of small particles (Evans *et al.*, 1975). The characteristic curves were also used to determine the relative doses necessary to give a film density of 1.0.

TABLE II

The imaging systems employed in the investigation

Film	Screen	Processing	
		Chemicals	Time (min)
Kodak Industrex C		Black and White RP	11·0
Agfa-Gevaert Medichrome	Ilford High Definition	Medichrome Colour	3·5
Du Pont Lo-Dose	Du Pont Lo-Dose	Black and White RP	1·5
Agfa-Gevaert Mamoray RP3	Agfa-Gevaert MR50	. .	1·5
Kodak MR-1	Kodak Min-R	. .	1·5
Trimax XM	Trimax αM	. .	1·5
Trimax XD	Trimax α4	. .	1·5

Data analysis

The radiographs of the test phantoms produced on the different imaging systems were numbered so that the observer, when reading the film, was unaware of the particular film/screen system used to produce that image. Medichrome film was, however, easily recognisable because of its characteristic blue colour.

The images were viewed using a standard Kodak X-ray illuminator which has a luminance of 1000 cd/m^2 measured with a Hagner photometer. Before reading the radiographs, observers were acquainted with the appearance of a signal plus noise and of background noise only. They also knew that no square contained more than one signal and that of the 100 test squares, 50 contained a signal and the remaining 50 noise only.

Observers were asked to express for each square the degree of certainty with which a signal could or could not be detected. Five levels of confidence were allowed. These were:

(1) almost definitely not present;
(2) probably not present;
(3) unsure;
(4) probably present;
(5) almost definitely present.

These results were marked on a report sheet which contained a reproduction of the test grid. In a completed report sheet, therefore, a number representing the observer's level of confidence was recorded in each of the 100 test squares. When categories (4) and (5) were employed the observer was also asked to mark the position of the signal as accurately as possible. This information was not required for the generation of the ROC curves but was included in an attempt to gauge the ability of the observer to reject artefacts. Throughout the periods of observation the viewing distance was not fixed nor was a time limit imposed upon the visual test procedures. The true positive probabilities were derived from those squares which actually contained a particle by expressing as a fraction of the total number of particles employed the numbers

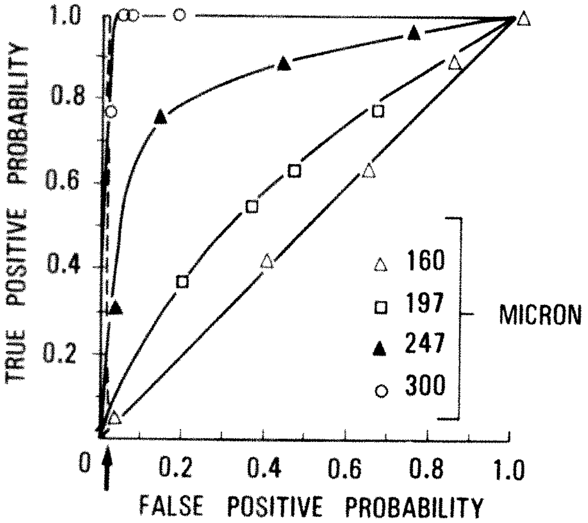

Fig. 1.

Single observer's ROC curves for different particle sizes imaged without scattering material with Trimax XD/α4 film/screen combination. The arrow and dotted line represent a 2% false positive rate.

obtained in each of the above categories. Similarly the false positives were derived by considering those squares which did not contain a particle. Full details can be found in Green and Swets (1966) and Goodenough *et al.*, (1974).

During the investigations the same four observers completed the total series of readings for the six phantoms, imaged with the seven systems, both with and without the scattering material—i.e. a total of 84 films per observer. In addition, some of the films were read by up to 15 observers in order to study the inter-observer variation.

By way of illustration Fig. 1 shows the results of an ROC analysis for one observer when the glass bead phantoms were imaged without the addition of scattering material using the 3M Trimax/XD α 4 film/screen combination. These curves demonstrate the changes produced in the ROC curve as signal detectability improves. Thus the ROC curve for the smallest particle size of 160 μm is roughly a straight line passing through the 0,0 and 1,1 points. In this situation, where the true positive detectability always equals the false positive level, the observer is clearly doing no better than guessing. As particle size increases there is a corresponding increase in the true positive levels of detection at lower false positive probabilities with a corresponding shift of the curves to the left.

To achieve a suitable degree of consistency for the ROC assessment of each imaging system four observers were involved in the whole investigation. To make the presentation of the results more concise and easily understood, these individual results were averaged for each system and the results presented in the remaining figures correspond to average detection rates for the four observers. A justification for this method of data analysis is presented in the subsequent discussion.

In the context of breast cancer screening programmes, it was decided that meaningful information could best be presented from these averaged ROC curve data by extracting true positive detection rates at a clinically useful rate of 2% false positives for each film/screen combination. The dotted line shown in Fig. 1 represents the true positive detection rate for each particle size assuming a false positive incidence of 2%. By repeating this process for each film/screen system curves were derived which relate the true positive detection rate at the 2% false positive level to the particle size and these are shown in Figs. 3 and 5.

Results

Scatter-free conditions

ROC curves averaged for four observers are shown in Fig. 2 for three of the imaging systems investigated. Figure 2a shows the results with the fast Trimax XD/α4 film/screen combination; Fig. 2b a medium speed system (Du Pont Lo-Dose); and Fig. 2c a slow high-dose mammographic system (Kodak Industrex 'C' film).

These ROC curves demonstrate the effect of a reduction in particle size on the signal detectability for each of these three imaging systems. They also demonstrate the level of confidence with which particles of a single size are detected using the different imaging systems. The Trimax system in Fig. 2a gave signal detectabilities which ranged from "purely random" for the 160 μm beads to "easily detectable" for the 400 μm beads. The Du Pont Lo-Dose system in Fig. 2b gave significantly higher true positive rates than the Trimax system at any given level of false positive detection, when bead sizes less than 300 μm were imaged. Even with this system, however, the smallest bead sizes were detected with only moderate levels of accuracy. The Kodak Industrex C system illustrated in Fig. 2c gave high true positive detection rates with corresponding low false positive rates for all signal strengths investigated.

Figure 3 records the true positive detection rates corresponding to a 2% false positive rate which were obtained from the ROC curves averaged for

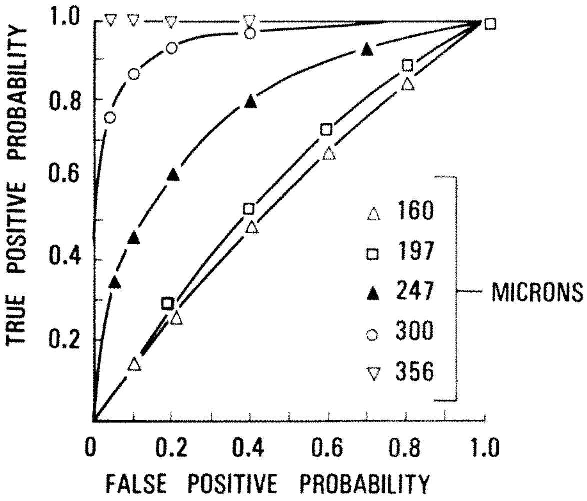

Fig. 2a.

(a) Averaged ROC curves for different particle sizes imaged without scattering material with Trimax XD/α4 film/screen combination.

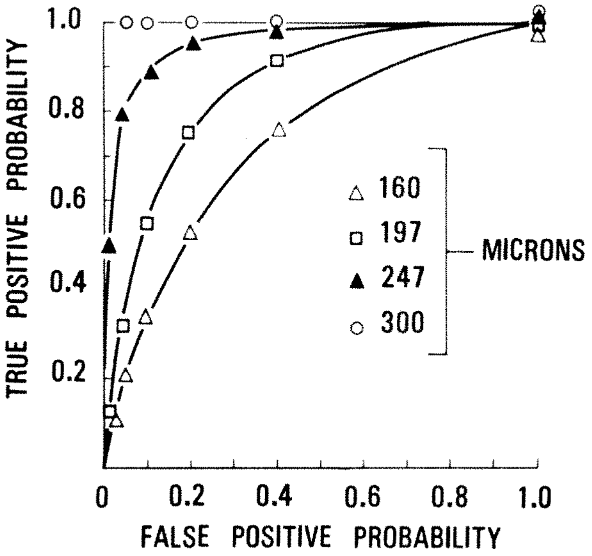

Fig. 2b.

(b) Averaged ROC curves for different particle sizes imaged without scattering material with Du Pont Lo-Dose system.

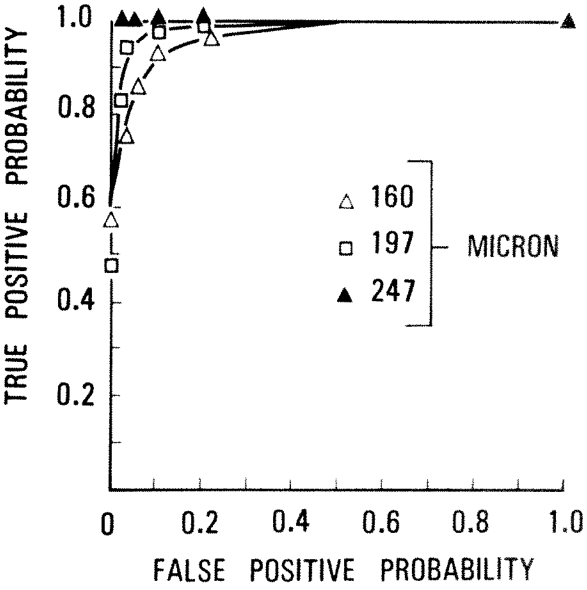

Fig. 2c.

(c) Averaged ROC curves for different particle sizes imaged without scattering material with Kodak Industrex C.

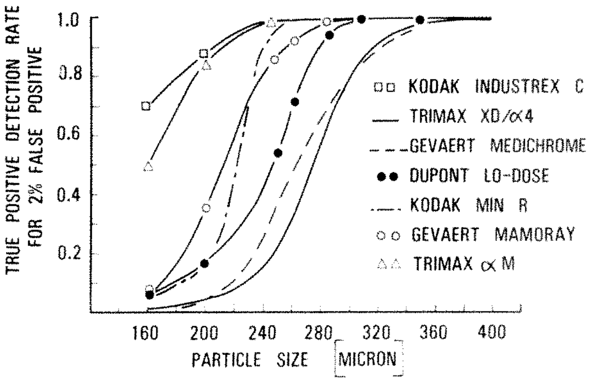

Fig. 3.

True positive detection rates, at the 2% false positive level, for different particle sizes imaged without scattering material.

four observers. It can be seen that the Kodak Industrex C system, which required the highest dose of the systems investigated, gave the highest true positive detection rate at the 2% false positive level for all bead sizes less than 300 μm. Even with the 160 μm bead its detection rate was still 70%. The Du Pont Lo-Dose system showed a steady reduction in true positive detection rate with decrease in particle size below 300 μm reaching the 50% level at 240 μm. By contrast with the Industrex system, at the 160 μm bead size its detection rate was only approximately 10%. The Trimax XD/α4 fast system has a similarly shaped curve with steady reduction in true positive detection rate for particle sizes below 380 μm. Its 50% level is at 280 μm particle size and for particles of 160 μm its true

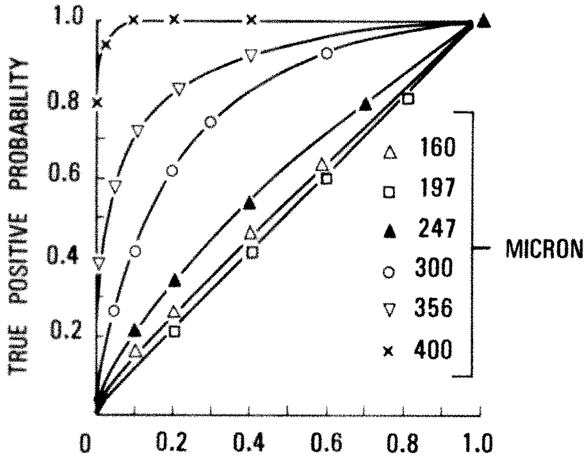

Fig. 4a.

(a) Averaged ROC curves for different particle sizes imaged with scattering material with Trimax XD/α4 film/screen combination.

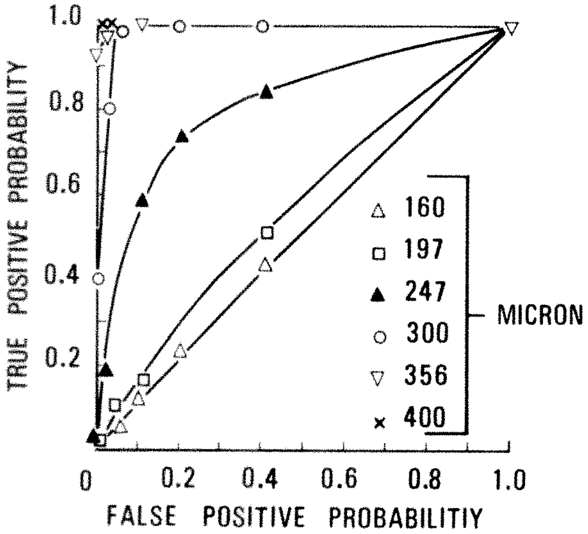

Fig. 4b.

(b) Averaged ROC curves for different particle sizes imaged with scattering material with Du Pont Lo-Dose system.

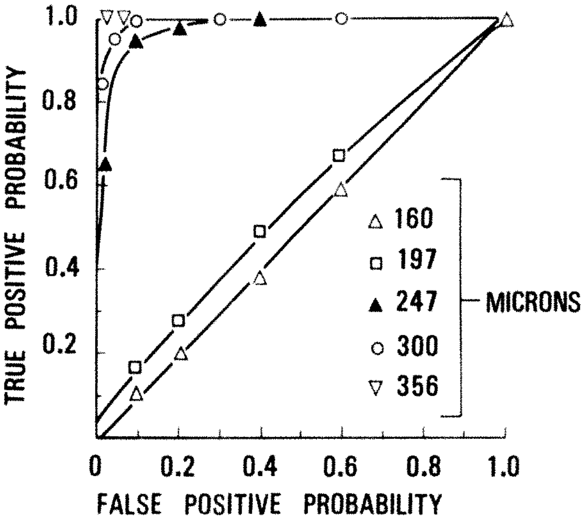

Fig. 4.

c

(c) Averaged ROC curves for different particle sizes imaged with scattering material with Kodak Industrex C film.

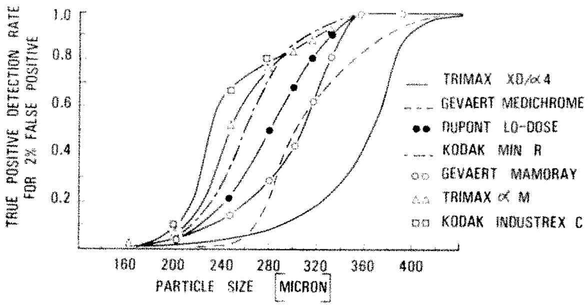

Fig. 5.

True positive detection rates at the 2% false positive level for different particle sizes imaged with scattering material.

positive detection rate was a mere 2%. The figure demonstrates in similar fashion the results for the other imaging systems investigated.

With addition of scattering material

Figures 4a, b and c demonstrate the results of the addition of tissue-equivalent scattering material. The presentation of the results is in exactly the same format as Fig. 2a, b and c. Comparison of Figs. 2a and 4a for the Trimax XD/*a*4 system show that for any given particle size the signal detectability has been reduced by the addition of scattering material. This was true for all the systems investigated. The extent of this overall decrease is demonstrated in Fig. 5 which should be

TABLE III

PERFORMANCE INDICES OF THE FILM/SCREEN COMBINATIONS WITH SCATTERING MATERIAL

Film	Screen	Relative dose to produce a density of 1·0	Particle size for 50% detection	Area under detectability curve
Trimax XD	Trimax α4	1	368	42·7
Agfa-Gevaert Mamoray RP3	Agfa-Gevaert MR50	4·5	308	69·3
Agfa-Gevaert Medichrome	Ilford High Definition	4·9	300	63·1
Kodak MR1	Kodak MIN R	5·4	260	88·7
Du Pont Lo-Dose	Du Pont Lo-Dose	6·5	280	82
Trimax XM	Trimax αM	17·5	248	91·8
Kodak Industrex C		22·7	230	97·3

compared with Fig. 3. For example, it can be seen that the signal detectability for Kodak Industrex film is reduced to 2% at the 160 μm bead size and to a 50% level at approximately 230 μm. The Du Pont Lo-Dose system again shows a gradual decrease commencing at the 340 μm bead size and reaching its 50% level at 280 μm. At the 160 μm particle size the true positive detectability has also reached 2% which corresponds to the random decision level. The Trimax XD/α4 system representing the fatest combination shows a rapid decrease beginning at the 420 μm bead size and reaching its 50% level at 370 μm. The particle sizes corresponding to the 50% true positive detection level when scattering material is included are shown in Table III together with the relative doses necessary to produce a film density of 1.0.

DISCUSSION

Predictions of image quality based solely upon objective measurements such as the modulation transfer function and Weiner spectrum of radiographic noise do not always correlate in a simple manner with subjective impressions of image quality (Goodenough *et al.*, 1974). The decision to use visual performance techniques based upon receiver operating characteristics arose from a recognition of the importance of this subjective element in radiological assessment and of the need to quantify it. In the assessment of mammographic image quality a recognized criterion of system performance is the delineation of micro-calcifications which are reported to occur in approximately 63% of histological examinations of carcinomas (Millis *et al.*, 1976). In our construction of a suitable test phantom we decided, therefore, to mimic this particular feature, using small soda-glass beads as micro-particles. Using these beads we could ensure that the particles were regular in shape and size. These requirements were not met in our preliminary experiments when powdered chalk and alumina were used.

Previous workers have assessed the ability of various imaging systems to detect both naturally occurring and simulated micro-calcifications (Evans *et al.*, 1975; Price and Butler, 1975; Millis *et al.*, 1976; Young, 1974). These studies, although enabling a semi-quantitative assessment of visual detection, do not permit a detailed analysis in terms of signal detection theory. For this to be achieved the assessment procedure should measure a false positive rate as well as the true positive detection rate. The ROC method used in our study has the particular advantage of presenting both true and false positive rates for each system at differing levels of signal strength.

It has been argued that clinically meaningful results can only be derived from biological test objects using actual micro-calcifications. Use of such a system, with the inevitable introduction of uncontrollable variables such as non-uniformity of particle size and shape and location, prevents a full statistical analysis. Similarly, use of mastectomy specimens would introduce the additional variable of non-uniformity of the background parenchymal breast structure. The influence of the background has been documented in relation to chest radiology (Revesz and Kundel, 1977).

This wide spectrum of tissue complexity does mean that our own results cannot be translated directly to the clinical sphere, but they have isolated in a manner capable of statistical analysis the ability of these particular imaging systems to reproduce small particles.

It is relevant to consider some of the factors upon which the accuracy of any visual detection experiment utilizing ROC analysis depends. They include:

(a) the size of the individual sample areas employed in the phantom;
(b) the ratio of the particle size to this sample area;
(c) the variation in particle sizes within a test phantom;
(d) the number of sample areas employed in the phantom.

These factors do not affect the relative assessment of performance presented in this study but they can affect the accuracy with which individual true and corresponding false positive detection rates can be measured. These factors will affect the overall accuracy of locating an individual ROC curve. In order to improve this accuracy, whilst accepting any variation produced by the other design factors listed above, the number of areas containing noise only and signal plus noise should be as large as possible. However, making this number too large can introduce an error into the analysis which depends upon the ability of the observer to maintain constant levels of decision thresholds during the period of an investigation (Goodenough, 1974). Our choice of 100 sample areas per image is a reasonable compromise.

In order to produce ROC curves which were representative of the imaging systems under investigation four observers assessed all the images. The ROC curves obtained for these observers were then averaged for each image. Several averaging processes were investigated and found to give reasonably similar results. The method employed throughout the investigation involved forming an average true positive probability amongst the individual observers' ROC curves for chosen false positive probabilities. Consequently the results presented in Figs. 3 and 5 correspond to average detection rates obtained from four observers.

The data points shown in Figs. 3 and 5 will have an uncertainty associated with their positions due to the uncertainties in ROC curve positions introduced by the factors mentioned previously. Estimating the contributions from individual factors to the overall uncertainty is not straightforward but a rough estimate can be obtained. The uncertainty in position of the ROC curve due to the limited number of trials or sample areas employed can be calculated. Assuming that the other factors contribute similar uncertainties, the total uncertainty associated with true positive detection rates shown in Figs. 3 and 5 can be estimated. Based on this approach the overall uncertainty will depend upon the actual value of true positive probability involved, ranging from roughly ±8% for 90% true positive detection, ± 12% for 50% to approximately ± 4% for 2% true positive detection.

An interesting feature of the results shown in Figs. 3 and 5 is the alteration in relative system performance when scattering material was employed. The reasons for this lack of uniform response are possibly two-fold. Firstly, it is recognised that systems do vary in their sensitivity to scattered radiation (Castle, 1975). Secondly, the characteristic curves of the imaging systems have different shapes so that it is to be expected that they will differ in their response to the "hardening" of the X-ray beam, with its consequent change in subject contrast, produced by the 4 cm of tissue equivalent scattering medium.

The apparent complexity of the results illustrated in Figs. 3 and 5 can be simplified by considering three major groupings. The industrial film represents a high radiation dose system which enables good visualization of even the smallest micro-particles in our series. The Trimax XD/α4 system, at the other extreme of very low radiation dose, has the worst performance in terms of ROC analysis. In between these two extremes the other systems display a similar range of performance and a final choice of system will be influenced by many other factors including the subjective appearance of the final image and the dose necessary to produce a suitable image.

In order to compare the abilities of the imaging systems to reproduce small particles, the results presented in Fig. 5 have been summarized in Table III. Also presented are the relative doses necessary to produce unit density. The particle sizes which correspond to a 50% true positive detection rate are presented and these decrease as the relative dose increases.

Because the particle sizes corresponding to a 50% detectability only represent a single point on each of the curves shown in Fig. 5, the area under each curve was measured for all particle sizes less than 440 μm. These results have also been included in Table III. The 440 μm particle size was chosen because all systems had achieved a 100% true positive detection rate at this size. The area under each curve represents an integrated true positive detectability over all particle sizes. This measure of system performance was found to increase as the relative dose increases, hence the overall small-particle detectability has increased as the dose increases. There is then a trade-off between dose and small-particle detectability.

Although the ability of an imaging system to record small particles is related to the dose necessary to produce an image, the results presented in Table III indicate that this ability does not increase linearly with the dose. There is evidence to suggest that this ability may depend upon (dose)^2 (Stapleton, 1976), which implies that large increases in the dose required will only produce proportionately small gains in signal detectability. This is, in fact, observed with the results presented in Table III.

The choice of a particular imaging system for mammographic investigations can be roughly divided into three categories: low, medium and high dose systems where the reproduction of micro-calcifications of different sizes will depend upon the speed of the system chosen. Whilst an argument can be made for the use of high-dose systems such as Kodak Industrex C and the Trimax αM system for single examinations of symptomatic patients, a slight increase in detection of small particles is achieved only at the expense of a considerable increase in dose to the patient. At the other end of the spectrum, the low-dose Trimax XD/α4 system results in an undesirably low detection rate for small particles. Systems for use in mammographic screening surveys of well-women should meet the requirement of a total skin dose of no more than 2 rad per two-view examination (Ellis, 1972). Within this framework the remaining four systems appear to provide an acceptable compromise between dose and quality.

ACKNOWLEDGMENTS

We are grateful to the manufacturers who supplied film/screen combinations to be used in this work. Our thanks are also due to our colleagues in the Department of Medical Physics and Bioengineering, Christie Hospital (Mr. J. B. Massey) and the Department of Radiology, Withington Hospital (Dr. G. Hartley) for help and encouragement during this work.

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Book review

A Programmed Introduction to Upper Gastro intestinal Radiology. By S. L. Gammil, pp. 226, illus., 1977 (Little Brown & Co., Boston), $17.50.

Dr. Gammil attended a convention on programmed learning in New Orleans in 1971 and subsequently a course on "how to program" taught by a Mr. Joe Mangiaraema of the University of South Carolina Medical School. This book is the fruit of their teaching. The book consists of a number of radiographs illustrating different lesion in the oesophagus, stomach and duodenum. Accompanying the radiographs is a short text consisting of a descriptive section, discussion and questions. The format is simple and meant to lead to involvement of the reader in the learning process. Unfortunately most of the discussion is so basic and the text so trite that a rage reaction may result. The book is of very limited appeal but may have some value for elective students who are spending a short period in an X-ray Department.

J. A. Gleeson.

1979, *British Journal of Radiology*, *52*, 634–641

The effect of recovery from potentially lethal damage on the determination of reoxygenation in a murine tumour

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ABSTRACT

The pattern of reoxygenation in the murine anaplastic MT tumour was investigated using the established method of determining the hypoxic fraction, at intervals after a priming X-ray dose, from test doses given either to unclamped or clamped-off tumours. Little reoxygenation was apparent whilst the tumour was increasing in size for 12–72 hours after a single dose of 20.3 Gy, but extensive reoxygenation was evident whilst the tumour was shrinking at nine days after a dose of 50 Gy.

However, the degree of reoxygenation may have been underestimated, especially after the smaller priming dose. This is because only the chronically hypoxic cells in this tumour have the ability to recover from potentially lethal damage (PLD) and so are more radioresistant than cells rendered acutely hypoxic by clamping. Because of this, even when tumours are clamped off during irradiation, the resulting survival curve is biphasic and the apparent effect of the clamp becomes a function of the X-ray dose used. The larger the dose, the smaller the observed effect of the clamp, so the greater the apparent hypoxic fraction and hence the smaller the apparent degree of reoxygenation.

Reoxygenation is the process by which the proportion of hypoxic cells in a tumour may be reduced between fractionated doses of X-rays. It has been shown that the degree and time-course of reoxygenation is a characteristic of different types of tumour, ranging from a poorly-reoxygenating osteosarcoma (van Putten, 1968) to a well-reoxygenating mammary carcinoma (Howes, 1969).

We report here on the pattern of reoxygenation in the anaplastic MT tumour which was determined using the method of tumour control described by Howes (1969). With this method, the hypoxic fraction is determined at intervals after a priming dose by a commonly used technique which assumes a simple two-compartment cell survival model in which the effect of oxygen is truly dose modifying: *i.e.*, the survival curves for oxic and hypoxic cells can be superimposed by simply altering the dose scale. Hence it is assumed that occlusion of the blood supply of the tumour ("clamped tumour") renders the tumour uniformly radioresistant and that the additional dose needed in clamped tumours relative to aerobic tumours ("unclamped tumours") gives a measure of the hypoxic fraction. If it is incorrect to assume that chronically hypoxic cells have the same radiosensitivity as those rendered acutely hypoxic, then this method will be in error.

This assumption is indeed incorrect for the MT tumour (McNally and Sheldon, 1977). Recovery from potentially lethal damage (PLD) in this tumour increased D_0 from 2.6 to 3.6 Gy, but only in the chronically hypoxic cells. This increase in D_0 did not occur in cells rendered acutely hypoxic at irradiation. Thus chronically hypoxic cells were more radioresistant than acutely hypoxic cells, and clamping did not give a uniformly resistant population.

The effect of this difference in radiosensitivity on the interpretation of data concerning reoxygenation in the MT tumour is discussed in the present paper.

METHODS AND MATERIALS

The tumour studied was the anaplastic MT tumour which has been maintained in inbred WHT/Ht mice at the Gray Laboratory since it arose spontaneously in 1964 in the same strain.

The experimental technique used has been described in detail previously (Sheldon and Hill, 1977a). Briefly, the tumours were implanted subcutaneously over the sacral region of the back, and were selected for treatment on attaining a size of 5–6 mm mean diameter. In order to irradiate the tumours, the mice were restrained without the aid of anaesthesia by being placed in individual lead boxes. These had a portion of the lead cut away so that the tumour was exposed to a horizontal X-ray beam (240 or 250 kV; 15 mA; HVL 1.3 mm Cu; dose rate about 3.9 Gy/minute). Halfway through each irradiation the boxes were turned through 180° to ensure a uniform X-ray dose throughout the tumour. Two types of restraining box were used. With single or priming doses when the tumours were only 5–6 mm, boxes with a small cut-out were employed because they afforded more protection to the intestine. For the second test doses in the reoxygenation experiments, boxes with a larger cut-out were employed to allow for the increased tumour volume. To render a tumour fully hypoxic, a D-shaped aluminium clamp was applied across the base of the tumour in order to occlude its blood supply. The clamp was applied ten minutes before, and left in place during, the irradiation.

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For the tumour control assay at 80 days after the mid-time of treatment, nodules of less than 2 mm were considered controlled ("cured") and those more than 4 mm as recurrent. Tumours between 2 and 4 mm inclusive were considered ambiguous and rejected from further analysis. These accounted for less than 1% of the treated tumours. The probability of local tumour control as a function of the X-ray dose, and the standard error of the mean (s.e.m.) of the dose required to control 50% of the tumours (TCD 50), were computed using the logit method of maximum likelihood (Suit *et al.*, 1965).

For the regrowth delay assay, three orthogonal diameters were measured thrice weekly after irradiation until the tumours had regrown to a mean diameter of 12 mm. The average time taken for tumours from each treatment group to grow from a geometric mean diameter of 5.5 to 10 mm was plotted against the X-ray dose.

The hypoxic fraction in previously untreated tumours was determined, by tumour control and regrowth delay assays, from the extra dose required to give the same response in clamped as unclamped tumours, *i.e.*, hypoxic fraction = exp. −(extra dose when clamped/D_0 for hypoxic cells).

The change in hypoxic fraction (*i.e.* reoxygenation) was monitored by tumour control assay whilst the tumour was increasing in volume at 12–72 hours after a single X-ray dose of 20.3 Gy, or when shrinking at nine days after a dose of 50 Gy. These priming doses of 20.3 and 50 Gy were given to unclamped tumours, whereas the subsequent test doses were given to half of the tumours while unclamped and half while clamped. The hypoxic fraction at the time of the test dose could, therefore, be determined as described above.

As the study progressed it was evident that clamping caused little or no increase in radioresistance of the tumour. Because of this, the possibility was examined that the clamping procedure itself might be sensitizing the tumours by, for instance, killing a vulnerable subpopulation. This was tested by observing the effect of the clamping procedure on (a) the growth rate of unirradiated tumours, (b) the regrowth delay after clamping for different periods of time before a dose of 41.6 Gy, and (c) the probability of tumour control when clamps were applied after irradiation. Experiment (b) was inadvertently done on a version of the tumour which was subsequently realized to have increased in sensitivity and hence was designated MT1 (Sheldon and Hill, 1977b).

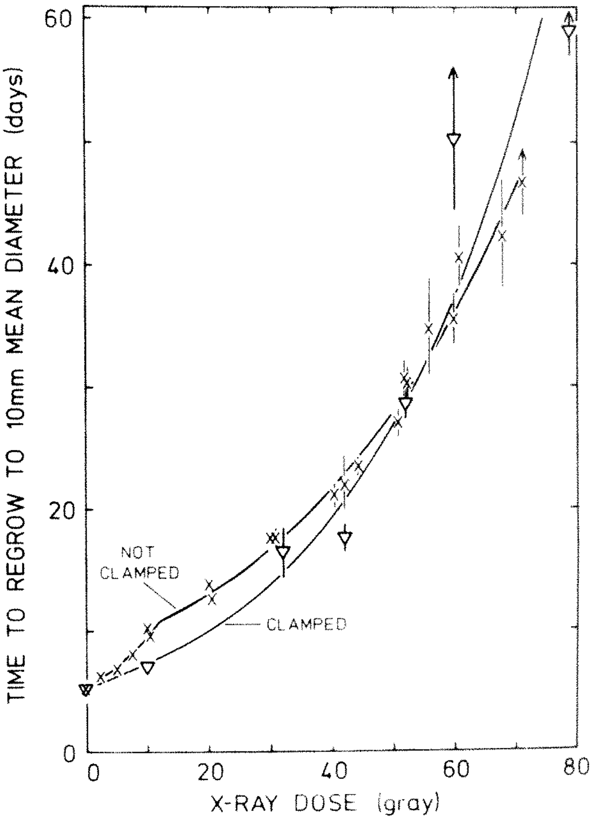


FIG. 1.
Regrowth delay after single dose of X rays to unclamped tumour (X, 227 mice) or clamped tumours (▽, 57 mice). The s.e.m. are shown only if they exceed the symbol size. Doses large enough to produce locally controlled tumours, for which no allowance has been made, are shown by the vertical arrows.

RESULTS

Tumour hypoxia

Figure 1 shows that the effect on regrowth delay of clamping during irradiation was not uniform. With small X ray doses which produced only a short delay, clamping did increase the radioresistance of the tumour. However, with larger X ray doses which produced longer delays, the effect of clamping diminished until, at a dose of 50 Gy, no effect at all was observed. The cross-over of the response curves at even higher dose levels is thought to be spurious. It is dependent on the two upper points for clamped tumours in which the radiation doses were large enough to produce 22 and 46% tumour control respectively, and so were beyond the ideal dose range for the regrowth assay.

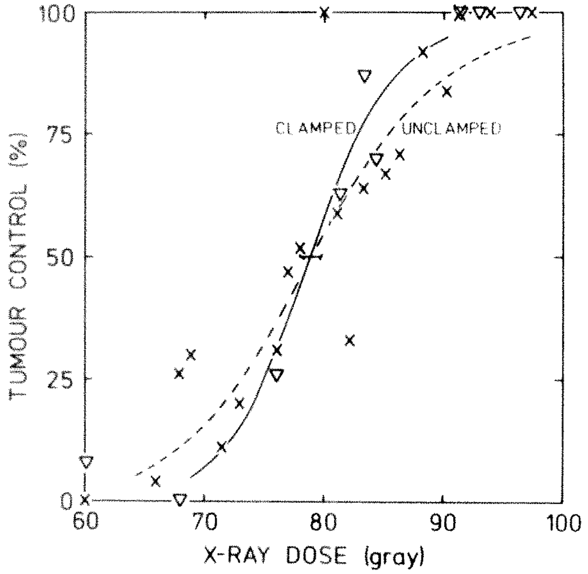


FIG. 2.

The probability of tumour control after single doses of X rays to unclamped tumours (X, 396 mice) and clamped tumours (▽, 134 mice). The TCD 50 values + s.e.m. are shown.

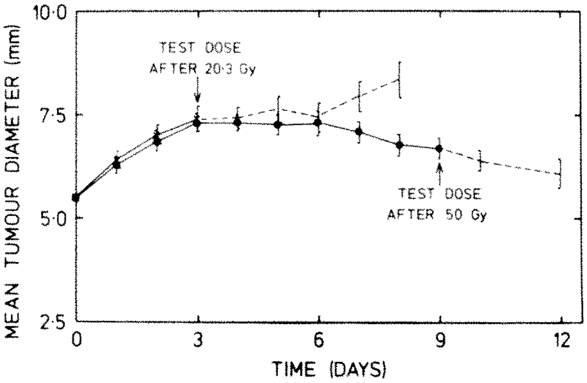


FIG. 3.

The growth pattern of the tumour after X-ray doses of either 20.3 Gy (X) or 50 Gy (●). The solid lines show the responses during the period used in the reoxygenation studies, when test doses were given 12–72 hours after a priming dose 20.3 Gy or nine days after a dose of 50 Gy. The dashed line shows the subsequent response when no test dose was given. The vertical bars represent the s.e.m. (13–16 mice per group).

Since the hypoxic fraction is conventionally derived from the increase in radioresistance due to clamping, then clearly that derived from Fig. 1 will depend on the delay selected. Assuming a D_0 of 2.6 Gy, as has been determined for this tumour when assayed *in vitro* (McNally and Sheldon, 1977), the estimated hypoxic fraction would vary from 2% at 11 days delay to 100% at 50 days delay (6 to 100% respectively if D_0 is 3.6 Gy). This dependence of the estimate of hypoxia on the extent of regrowth delay will be shown later to be due to recovery from PLD in the chronically hypoxic cells.

Figure 2 shows the effect of clamping on the probability of tumour control. The single dose of X rays required to eradicate 50% of the tumours in their normal clamped state was determined in ten experiments performed over a three year period. The resulting TCD 50 values (77.9, 81.2, 78.2, 76.9, 80.2, 76.4, 84.7, 73.8, 72.7 and 77.9 Gy) showed no trend with time and were all within two standard deviations of the mean TCD 50 of 78.0±3.5 Gy (±1 standard deviation). Therefore, they are considered to be random values from the same tumour population and so the data from these ten experiments have been combined to give a more accurate estimate of the TCD 50: 78.9±0.7 Gy (±s.e.m.). This value is used here as the control, and is not significantly different from that of 78.8±0.9 Gy for clamped tumours. This indicates that the tumours are normally fully hypoxic. Assuming a D_0 of 3.6 Gy, the minimum hypoxic fraction compatible with the limits of the standard error of the means is 66% (56% if D_0 is 2.6 Gy).

Reoxygenation study

The change in size of the tumours after doses of 20.3 or 50 Gy is shown in Fig. 3. In both cases there was a progressive increase in size for three days, after which no change occurred for a further three days. The tumours then either regrew (after 20.3 Gy) or shrank (after 50 Gy). The reoxygenation study was done during both the initial period of increase in size (*i.e.*, 12–72 hours after a priming dose of 20.3 Gy) and the subsequent period of shrinking (*i.e.*, at nine days after a priming dose of 50 Gy).

The test dose required to achieve 50% tumour control after a priming dose of 20.3 Gy increased up to 12 hours because of repair processes (Fig. 4). Beyond this time there was no significant change in the curve for clamped tumours suggesting that no repopulation had occurred. However, the curve for unclamped tumours showed a trough at 24 hours followed by a gradual rise to 72 hours. As the

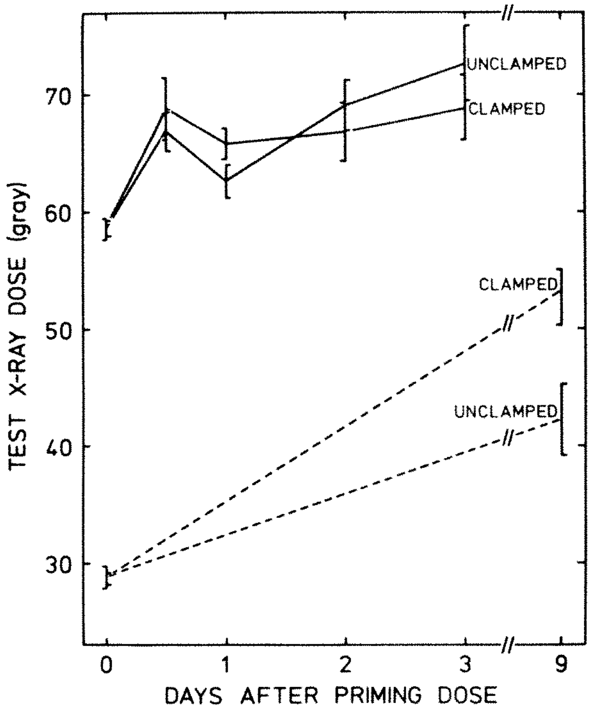


FIG. 4.

The extra (*i.e.* test) dose required to control 50% of tumours 12–72 hours after a priming dose of 20.3 Gy (full lines) or 9 days after a priming dose of 50 Gy (dashed lines). The priming doses were given to tumours in their normal unclamped state, the test doses to either unclamped or clamped tumours. (*NB* 20.3 or 50 Gy was deducted from the single doses given to the controls irrespective of whether or not they had been clamped). The vertical bars represent the s.e.m. (51–82 mice per TCD 50 excluding zero time controls derived from Fig. 2).

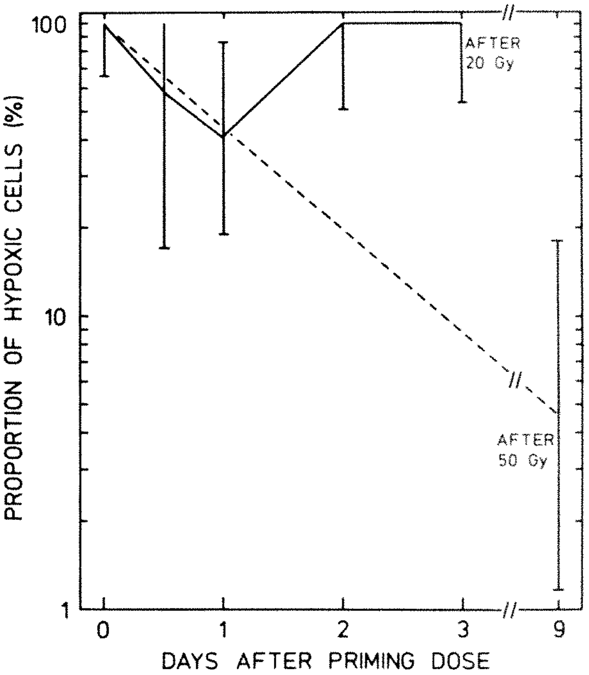


FIG. 5.

The apparent proportion of hypoxic cells 12–72 hours after a priming dose of 20.3 Gy or nine days after a priming dose of 50 Gy. Vertical bars represent the s.e.m. ranges.

displacement of the clamped from the unclamped points conventionally indicates the fraction of hypoxic cells, this trough at 24 hours indicates a phase of increased radiosensitivity because of reduced hypoxia resulting from reoxygenation. Similarly, reoxygenation was indicated at nine days after a priming dose of 50 Gy because the test dose required to achieve TCD 50 was considerably lower in unclamped than clamped tumours.

Figure 5 shows the proportion of hypoxic cells, calculated by the conventional method described above, at the time of the test doses. At 24 hours after a priming dose of 20.3 Gy, the hypoxic fraction had apparently been reduced from 100 to 41%, suggesting some reoxygenation. However, a horizontal line could be drawn through the error bars suggesting that in fact no significant reoxygenation had occurred up to 72 hours. At nine days after a dose of 50 Gy, the hypoxic fraction had apparently decreased significantly from 100 to 5%, suggesting extensive reoxygenation.

TABLE I

THE TIME TAKEN FOR MT1 TUMOURS TO GROW TO 10 MM MEAN DIAMETER AFTER CLAMPING FOR VARIOUS PERIODS OF TIME BEFORE A SINGLE X-RAY DOSE OF 41.6 GY TO CLAMPED TUMOURS.

Period of clamping (min)			Regrowth delay (days) ± s.e.m.
Before irradiation	During irradiation*	Total	
5	12	17	22.6 ± 1.5
15	12	27	22.8 ± 0.8
30	12	42	22.6 ± 0.7

*Includes time for turn around at half doses.

Effects of the clamping procedures.

The effect on the growth of unirradiated tumours of applying the clamps for 30 minutes was a slight delay in the first 24 hours followed by acceleration (Fig. 6). However, this effect was small and of dubious significance.

Table I shows the effect of applying clamps for differing periods of time on growth delay of the more radiosensitive tumour, MT1. The delay was

23 days irrespective of whether the tumours had been clamped for a total of 17, 27 or 42 minutes.

The effect on the probability of tumour control of applying the clamps for 30 minutes immediately after the end of irradiation was to reduce the TCD 50 from 78.9 to 74.1 Gy (Fig. 7). At first appraisal this does suggest that clamping after irradiation can increase the sensitivity of the tumour by 6%. However, this difference is not significant because the TCD 50 of 74.1 Gy is within two standard deviations of the mean TCD 50 of 78.0 Gy derived from the 10 separate control experiments.

DISCUSSION

Conventional assessment.

Reoxygenation has been reported to occur in tumours of different morphology. It has been observed in C3H mammary carcinomas (Suit and Maeda, 1967; Howes *et al.*, 1972; Fowler *et al.*, 1975), the fibrosarcomas KHT (Kallman, 1972) and RIB5 (Thomlinson, 1968), the carcinomas KHJJ (Kallman, 1975) and NT (Denekamp and Harris, 1976), a bone sarcoma (Denekamp and Harris, 1976) and, albeit to a limited extent, the osteosarcoma C22LR (van Putten, 1968).

The mechanism of reoxygenation is uncertain, but it is generally considered to occur in two phases. A previous dose of X rays may either damage cells so that their oxygen consumption is reduced (which would permit oxygen to diffuse further from the capillaries) or it may kill cells which, if removed, would reduce the intercapillary distances. It has been postulated that this second phase may be accompanied by tumour shrinkage (Thomlinson, 1970; Denekamp, 1972). This postulate is compatible with the present work in which the extent of reoxygenation of the anaplastic MT tumour, assessed by the conventional method, was greater when the tumour was shrinking (at nine days after an X-ray dose of 50 Gy) than when increasing in volume (12–72 hours after a dose of 20.3 Gy). However some curious observations were made in the present work. The effect of occluding the blood supply of the tumours by clamping was dose dependent on regrowth delay (Fig. 1) and nil on tumour control (Fig. 2). Further, the test doses to achieve TCD 50 at two and three days after priming doses of 20.3 Gy were greater (albeit not significantly) for unclamped than clamped tumours (Fig. 4). Although clamping is a commonly used technique (Suit and Maeda, 1967; Thomlinson, 1968; Howes, 1969; Fowler *et al.*, 1975; Denekamp and Harris, 1976), the above mentioned curious observations could be explained if clamping, apart from producing the desired increased radioresistance due to complete hypoxia, could also simultaneously sensitize the tumour by, for instance, causing the death of a vulnerable sub-population. This could result from an accumulation of metabolic toxins, or by rendering normally hypoxic cells anoxic. However, clamping produced little, if any, change in the growth of unirradiated tumours (Fig. 6), clamping for 17 or 42 minutes gave the same regrowth delay (Table I), and no significant change in TCD 50 was observed when clamps were applied after irradiation (Fig. 7). Hence these experiments produced no significant evidence to support the hypothesis that the clamping procedure could be sensitizing the tumour. It will be shown below that the above-mentioned curious observations can be explained by the occurrence of PLD in the chronically hypoxic cells.

Effect of recovery from PLD.

The proportion of hypoxic cells in the MT tumour has previously been reported to be 5% when determined by *in vitro* assay after irradiation *in vivo*, or 100% (as here) when determined by tumour control assay (McNally and Sheldon, 1977). This discrepancy in the estimates of the hypoxic fraction was attributed to the ability of the chronically hypoxic cells alone to recover from PLD.

It was demonstrated, by assaying *in vitro* after irradiation *in vivo*, that three subpopulations could exist as shown in Fig. 8: well oxygenated sensitive

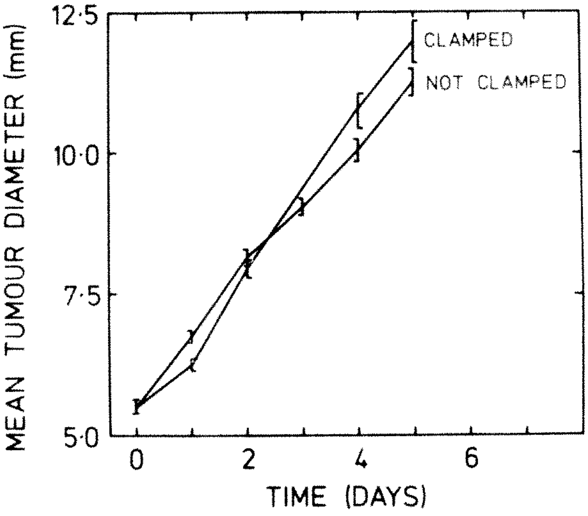


FIG. 6.

The effect of clamping for 30 minutes on the growth of otherwise untreated tumours. Vertical bars represent the s.e.m. (ten mice per treatment).

cells ($D_0=1$ Gy, $n=25$), resistant cells rendered acutely hypoxic by clamping ($D_0=2.6$ Gy, $n=25$), and extremely resistant chronically hypoxic cells which alone had the ability to recover from PLD ($D_0=3.6$ Gy, $n=10$). This model predicted that the TCD 50 of 78.9 Gy would reduce the surviving fraction of cells by 10^9, whereas calculation of the cell density from histological sections, using red blood cells as the standard (7.2 μm diameter), showed that the tumour could not contain more than 10^7 cells at the size used. Thus the *in vitro* data did not quantitatively fit the tumour control data, although they went some way towards it because the simple assumption of a uniform resistance in all cells when a clamp was applied gave a larger discrepancy.

Even with a clamp, a biphasic curve would result, although the breakpoint towards the more resistant chronically hypoxic cells would then occur at a higher dose. According to Fig. 8 the breakpoint occurred at 5 Gy in aerobic tumours and at 30 Gy in clamped tumours. At doses above 30 Gy the clamped and aerobic curves became superimposed because both were dominated by the chronically hypoxic cells. The estimated hypoxic fraction, therefore, depended on the dose or survival level at which it was measured. According to Fig. 8 it would be correct at 5–7 Gy, but too high at all larger doses.

This is supported by the regrowth delay curves determined in the present work after unclamped or clamped irradiation (Fig. 1). The hypoxic fraction, determined from the displacement of the clamped from the non-clamped response curve, was 2% at the 10 Gy unclamped dose level, but reached 100% at the 50 Gy dose level. The cross-over of these curves at high doses is probably not significant.

The effect that this dependence on dose of the estimated hypoxic fraction would have on the assessment of reoxygenation is shown qualitatively in Fig. 9. The normally oxic cells are assumed to be effectively eliminated by priming doses of 20.3

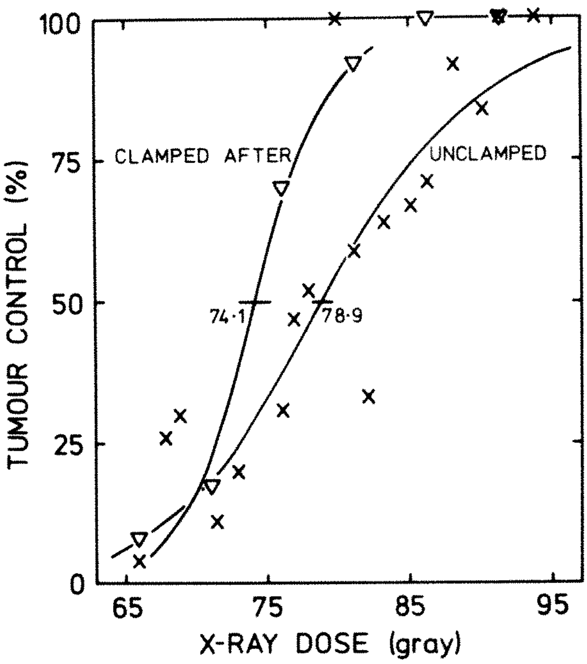


Fig. 7.

The effect on the probability of tumour control of applying clamps for 30 minutes immediately after the end of irradiation with a single dose of X rays. ▽, clamped tumours (68 mice); X, unclamped tumours (396 mice). TCD 50± s.e.m. are shown.

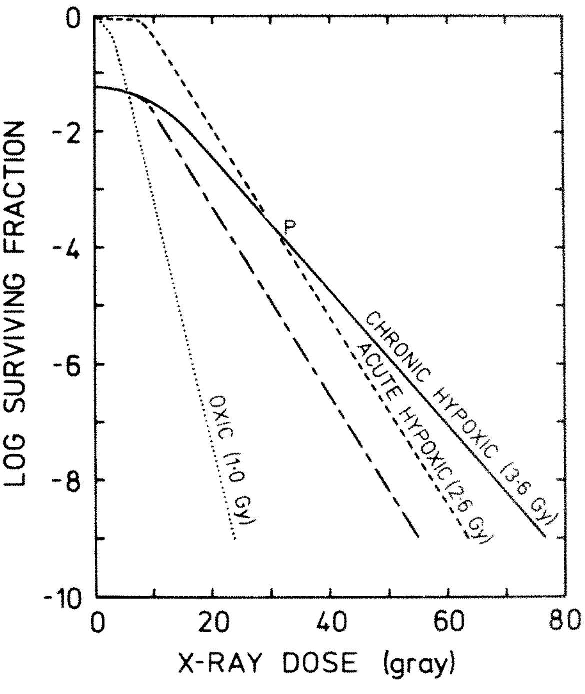
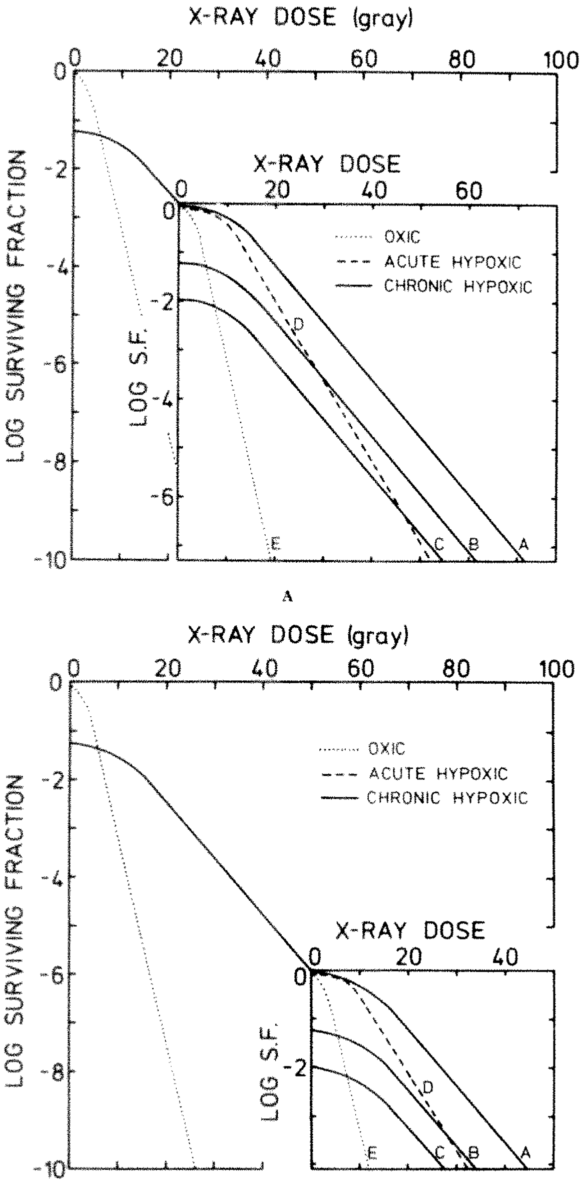


Fig. 8.

Cell survival curve of the MT tumour derived from *in vivo/in vitro* assay (redrawn from McNally and Sheldon, 1977). Three subpopulations can exist: normally oxygenated cells, cells rendered acutely hypoxic by clamping and the chronically hypoxic cells which can recover from PLD. The variable dashed line (– – –) shows the response if insufficient time is permitted for recovery from PLD to occur (~2 hours). Because the chronically hypoxic cells are more radioresistant than acutely hypoxic cells, the response is biphasic (breakpoint P) even when irradiated while clamped. D_0 values are shown.

(Fig. 9A) or 50 Gy (Fig. 9B). The subsequent response of the tumour would, therefore, be solely dependent on the behaviour of the surviving chronically hypoxic cells. If they died of their hypoxia, or were reoxygenated, or lost their ability to recover from PLD as a result of being reoxygenated, the tumour radiosensitivity would increase. However, in all cases time would be an important factor.



A

B

Fig. 9.

Survival model showing the effect of recovery from PLD by the chronically hypoxic cells on the estimation of reoxygenation after a priming dose of (A) 20.3 Gy or (B) 50 Gy. Curves A, B and C refer to 0, 95 and 99% reoxygenation respectively. The model shows that no reoxygenation or 100% reoxygenation would be accurately determined, but partial reoxygenation would probably be underestimated (see text).

If at the time of the test dose no reoxygenation had occurred, the survival would be dependent only on the remaining chronically hypoxic cells. Assuming sufficient time (2 hours) had elapsed for recovery from PLD to be complete, the response would be that on the far right (solid curve A). All cells being hypoxic, no effect of clamping would be observed, suggesting correctly that no reoxygenation had occurred. Similarly, if 100% reoxygenation had occurred then the response to the test dose under aerobic conditions would be that to the far left (dotted curve E). If all cells were oxic, the full anticipated effect of clamping would be observed (dashed curve D) and so complete reoxygenation would, quite correctly, be suggested.

If only partial reoxygenation had occurred, however, and if the newly reoxygenated cells had lost their ability to recover from PLD, the response would be more complex. For example, if 95 or 99% of the cells had been reoxygenated, the initial response to the test doses would be described in Fig. 9 by oxic curves indistinguishable from curve E if irradiated under aerobic conditions, or by acutely hypoxic curves indistinguishable from curve D if irradiated clamped off. In all cases the ultimate response would be dominated by either the 5% (solid curve B) or the 1% (solid curve C) of chronically hypoxic cells. Thus the responses would be biphasic, irrespective of whether or not a clamp had been applied. The apparent effect of clamping would be dependent on the size of the test dose: the larger the dose the smaller the change caused by clamping and so, as described above, the greater the apparent hypoxic fraction and hence the less the apparent degree of reoxygenation.

Furthermore, the breakpoint for 99% reoxygenation (intersection of curves D and C) would be displaced further to the right than for 95% reoxygenation (intersection of curves D and B). Because of this, clamping will have a more noticeable effect with test doses given after a large priming dose (Fig. 9B), than a small one (Fig. 9A). Consequently the underestimation of reoxygenation is more likely to be greater after a small than a large priming dose.

Conclusions

The effects that recovery from PLD by the chronically hypoxic cells alone may have on the estimation of the degree of reoxygenation are:

(i) nil if reoxygenation had not occurred;

(ii) nil if complete reoxygenation had occurred (assuming that recovery from PLD was immediately lost by the reoxygenated cells);

(iii) an underestimate if only partial reoxygenation had occurred;

(iv) the underestimate would be greater after a small than after a large priming X-ray dose.

Consequently, the apparent reoxygenation computed here by the conventional analysis requires reappraisal. Little reoxygenation was observed while the tumour was increasing in size 12–72 hours after a dose of 20.3 Gy, but extensive reoxygenation was evident when the tumour was shrinking 9 days after a dose of 50 Gy. Since some reoxygenation was observed, it is probable that the true extent was underestimated in both cases, but especially after the small priming dose of 20.3 Gy. Thus, from this work no quantitative conclusion can be made as to the importance of tumour shrinkage on the degree of reoxygenation achieved.

It is suggested that estimates, derived by artificially producing full hypoxia, of reoxygenation in other tumours should be treated with reserve unless it has been shown that their chronically hypoxic cells do not differ from their acutely hypoxic cells in radiosensitivity.

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Recovery from sublethal damage by acutely hypoxic tumour cells *in vivo* and *in vitro*

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ABSTRACT

The ability of acutely hypoxic tumour cells to recover from sublethal damage following irradiation *in vivo* and *in vitro* has been measured using a single tumour system. The methods of assay were tumour growth delay, local tumour control and tumour cell survival *in vitro* following treatment *in vivo* or *in vitro*. Tumours *in vivo* or cells *in vitro* rendered acutely hypoxic during irradiation were irradiated with either single doses or two doses 24 hours apart. Cells left *in situ* had a greater capacity for recovery than those treated either *in vivo* or *in vitro* and then assayed *in vitro*. It is suggested that tumours may not show a systematically reduced capacity for recovery relative to normal tissues, unless chronically hypoxic tumour cells have a reduced capacity for recovery and determine the response. However, the results imply that deductions as to the ability of tumour cells to recover from sublethal damage (whether chronically hypoxic or not), which rely on *in vitro* assays, may underestimate the extent of recovery.

The role of the intercellular environment in determining a cell's response to radiation is still poorly understood, particularly for cells *in vivo*. The study of cells grown either as monolayer cultures or as multicellular spheroids has clearly demonstrated the importance of the local environment in determining cellular radiosensitivity. Cells in three dimensional contact with each other have a greater capacity to absorb and recover from sublethal radiation damage than single cells (Sutherland and Durand, 1976). Non-dividing plateau phase cells differ in their radiation response from cells in logarithmic growth as a result of both differences in age distribution (Hahn and Little, 1972) and in the degree of intercellular contact (Durand and Sutherland, 1973; McNally and de Ronde, 1976).

For a number of normal tissues there are direct quantitative methods for determining the response of their cells to radiation (see Fowler and Denekamp (1977) for a review). In general, cells in tissues show a greater ability to recover from sublethal damage than cells *in vitro* (Phillips, 1972), with the exception of the cells of the haemopoietic system. This could reflect differences in the intercellular environment analogous to the differences between single cells and cells in spheroids. For tumours, however, such direct *in situ* methods of assay are not available. Indirect methods in which cells are left *in situ* rely on measurements of tumour growth delay or of the probability of tumour sterilization. Alternatively, tumours can be excised after treatment and the response of their cells assayed by the end-point dilution technique by injecting them into animals (Hewitt and Wilson, 1959), or by plating the cells *in vitro* (Barendsen and Broerse, 1969). These latter methods measure effects on tumour cells directly. If one wishes to compare tumours and normal tissues it is important to determine whether or not methods of assay in which tumour cells are removed from their normal environment after irradiation accurately reflect the course of events in the undisturbed tumour.

In this paper we report experiments in which comparisons were made of the ability of cells from one type of murine tumour to recover from sublethal damage either when left *in situ* (using tumour growth delay or sterilization as the endpoints), or when plated *in vitro* following irradiation *in vivo*, or when irradiated and assayed *in vitro*.

MATERIALS AND METHODS

The tumour used for this study was derived from a serially transplanted fibrosarcoma of spontaneous origin, growing in WH/Ht mice at the Gray Laboratory and provided by Dr. H. B. Hewitt. An *in vitro* cell line was established from one of these tumours. After a period of about 18 months' adaption, the cells of this new line, previously denoted Fib/T (George *et al.*, 1976; McNally *et al.*, 1978), but now called WHFIB, formed colonies with a plating efficiency of 50 to 90% when plated onto a "feeder layer" of 5×10^4 radiation-killed cells in alpha medium (Flow Laboratories), in a 50 mm diameter petri dish. At this stage, a large number of cells of this established line of cultured tumour cells in complete medium plus 10% dimethyl sulphoxide (DMSO) were frozen down and stored in 2 ml ampoules in liquid nitrogen. Cells are now only passaged *in vitro* a further 18 to 20 times from this stage. They are then discarded and a new culture established from the frozen cells. This procedure has ensured that the characteristics of the cell line and the tumours derived from it have remained constant.

Experimental tumours were obtained as follows. About 10^5 cells from the *in vitro* cell line were injected subcutaneously into a WHT/Ht mouse. The resulting tumour reached a mass of 0.2–0.3 g within 20 days. This was then used as a donor to provide experimental tumours by transplanting small pieces by trochar subcutaneously into a large number of mice. Details of this procedure and of the methods used to irradiate the tumours have been described previously (George *et al.*, 1977).

Tumours were irradiated in pentobarbital- anaesthetized mice with 250 kV X rays, HVL 1.3 mm Cu, at a dose rate of 3.2 Gy/min, when they had reached a diameter of 7.5 ± 1 mm. In order to avoid problems due to reoxygenation between two radiation doses, which would make it difficult to determine the extent of recovery, tumours were rendered hypoxic during irradiation by applying a clamp ten minutes before the start of irradiation. While this procedure meant that the response of acutely (as well as chronically) hypoxic cells was being measured, and such cells are probably not important in determining the response of a tumour to radiotherapy, by dividing the result by the appropriate oxygen enhancement ratio the response of the oxic cells can be deduced. Also, such a procedure allows comparisons with normal tissues to be made. For measurements of growth delay, tumours were measured at least three times per week over three mutually perpendicular diameters until they reached a mean diameter of approximately 11.5 mm, when the animals were sacrificed. The geometric mean diameter was calculated for each mouse tumour for each measurement and hence the time required to increase in diameter by 2 mm from the size at irradiation. The average time and standard error were calculated for each group of mice receiving the same treatment. This mean time was then plotted against radiation dose to obtain dose-effect curves.

In order to assess whether or not tumours were sterilized when using larger doses of radiation, mice were examined at regular intervals for up to 120 days after irradiation. At that time, mice having no measurable tumours were deemed to have been cured. The TCD_{50}, the dose to cure 50% of the animals, and its 95% confidence limits, were then calculated using a computer program based on the logit method for maximum likelihood (Suit *et al.*, 1965).

Tumour cell survival *in vitro* following treatment *in vivo* was determined by killing mice by neck luxation immediately after irradiation, excising the tumours and preparing single cell suspensions as previously described (McNally, 1972a). A known number of cells was then transferred, in alpha medium plus 15% fetal calf serum and antibiotics, to 50 mm plastic petri dishes containing 5×10^4 radiation sterilized "feeder" cells. Four dishes were used for each sample. They were incubated for 8 to 10 days at 37°C in a humidified atmosphere of 5% CO_2 in air. Colonies were then stained and counted.

For cells treated *in vitro*, a suspension was prepared either from an unirradiated tumour or from cells from a stock culture of the *in vitro* cell line in logarithmic growth. Approximately 2×10^5 cells per dish were pipetted into 50 mm glass petri dishes and left to attach overnight. The cells were then irradiated with 250 kV X rays (HVL 1.5 mm Cu, dose rate about 3.3 Gy/min) at room temperature, in an irradiation chamber which could hold up to 30 dishes. Humidified air or nitrogen, plus 5% CO_2, could be passed over the dishes which contained about 3 ml of medium. Radiobiological hypoxia was produced by flushing with the nitrogen-CO_2 mixture for 30 minutes before and during irradiation at a rate of about 6 litre/min. For split-dose experiments, cells were exposed to a first dose in hypoxia, returned to the incubator in air, and exposed to a second dose in hypoxia 24 hours later. After irradiation was completed the cells were removed from the petri dishes by trypsinization, counted, diluted and pipetted into plastic petri dishes containing "feeder" cells and incubated for eight to ten days for colony formation.

Results

Tumour growth delay

Figure 1 shows the time for tumours to grow from irradiation size (7.5 ± 1 mm) to a size 2 mm greater as a function of the total dose of radiation. The errors bars represent one standard error of the mean. Between seven and nine mice were used for each dose group. Unirradiated tumours (12 mice) took 3.5 days to increase in diameter by 2 mm, corresponding to a volume doubling time of about 3.4 days. This was typical of values that had been obtained previously. Clamping tumours twice at intervals of 24 hours had no significant effect on tumour growth. The arrow on the highest dose point in the two-fraction experiment indicates that, at this dose, one mouse was cured. This was not included in the analysis. The lines through the data points in Fig. 1 have been fitted by eye and indicate that above a single dose of 30 Gy the displacement between the curves was constant and equal to about 13 Gy.

Tumour sterilization

Table I shows the proportion of mice cured when larger doses of radiation were delivered to clamped

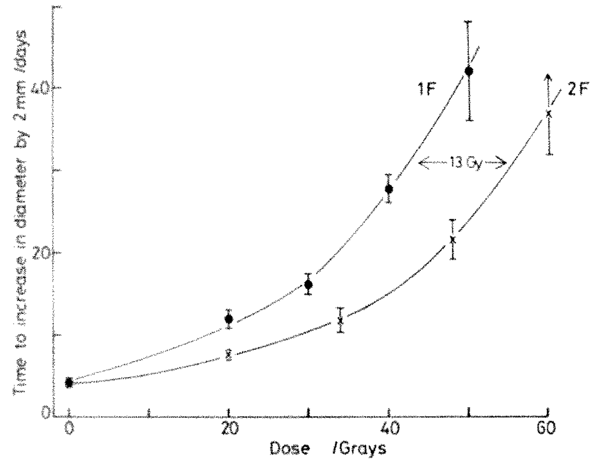

Fig. 1.

Dose response curves for the WHFIB tumour using tumour regrowth after irradiation. Error bars show ± standard error of the mean. Tumours were irradiated with either single doses or two doses 24 h apart and were clamped at the time of irradiation.

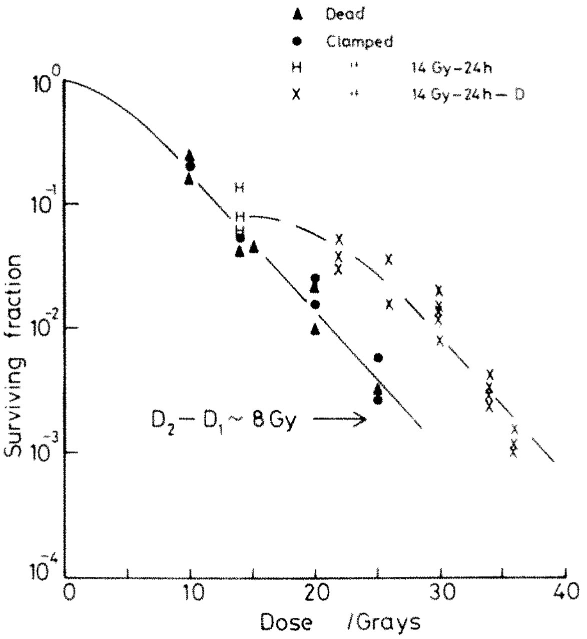

Fig. 2.

Survival curves for tumour cells irradiated *in vivo* and assayed *in vitro*. For single doses tumours were irradiated either in dead animals (▲) or when clamped (●). For split doses (X) tumours were exposed to a first dose of 14Gy and to graded second doses 24 h later. They were clamped for both doses. Clamped tumours were also exposed to a dose of 14 Gy and then left in the animal for 24 h (unclamped) before excising and assaying for cell survival (H).

TABLE I

The proportion of mice cured by a single dose or two doses of radiation 24 hours apart. Tumours clamped at the time of irradiation

Total Dose (Gy)	Total mice	No. cured	% cured
single doses			
46	12	0	0
54	10	0	0
62	11	1	9
70	13	11	85
split doses			
50	11	2	18
60	12	0	0
70	13	1	8
80	13	4	31
90	9	9	100

tumours either as a single dose or as two equal fractions 24 hours apart. When two fractions were given, two out of eleven mice were cured at the lowest total dose used (50 Gy). This was not expected, as 54 Gy in a single dose or 60 Gy in two equal fractions did not cure any mice (Table I). There is no obvious explanation for this discrepancy. It was not possible to repeat the experiment because the mouse colony was being converted to "specific pathogen free" status and no more experimental mice were available at this time. For the computer analysis of the results the 50 Gy fractionated result was not included, since if it was used the computer program gave a poor fit to the data, although there was little effect on the calculated TCD_{50}. The TCD_{50} for a single dose was 66.5 Gy (95% confidence limits 65.2 Gy to 67.8 Gy) and for a two-fraction dose was 81.2 Gy (95% confidence limits 79.6 to 82.9 Gy), giving a D_2–D_1 of 14.7 Gy, with 95% confidence limits of 12.6 to 16·8 Gy. (If the 50 Gy two-fraction dose data point was included, the calculated two-fraction TCD_{50} was 81.9 Gy).

Tumour cell survival in vitro *following irradiation* in vivo

Figure 2 shows survival curves for tumour cells irradiated in tumours obtained as previously described and then assayed *in vitro*. Tumours were either irradiated when clamped or in animals that had been killed ten minutes previously, and then immediately excised, or exposed to a first dose of 14 Gy and then to graded doses 24 hours later, with clamps applied for both irradiations, and excised immediately after the second dose. The lines through the points have been fitted by eye. There was no difference in the survival of cells from tumours that were clamped or that were in dead

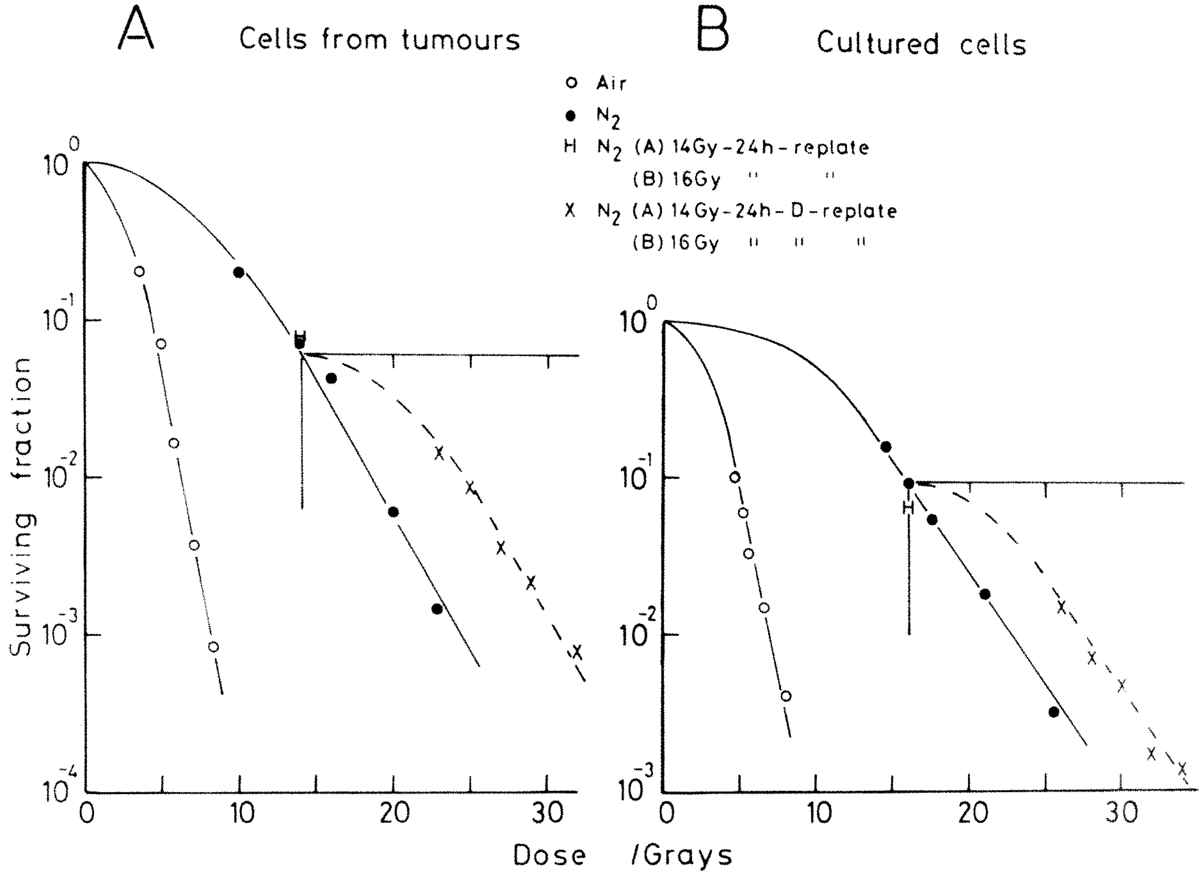

FIG. 3.

Tumour cell survival *in vitro* after irradiation *in vitro*. Cells were plated from either a tumour (A) or a culture in logarithmic growth (B) and left to attach for 18 h. They were then irradiated with single doses in air (O) or hypoxia (●) and with two doses 24 h apart in hypoxia during irradiation (X). The priming doses were 14 Gy for cells from tumours (A) and 16 Gy for cultured cells (B). Cells were replated after treatment to assess their colony forming ability. Cells were also held for 24 h after the priming dose before replating (H).

animals when exposed to single doses. The single dose survival curve (for acutely hypoxic cells) had a D_0 of about 4 Gy, an extrapolation number of 2 and D_q of about 3 Gy. Above a total dose of 25 Gy the "fractionated" survival curve was displaced from "the single dose" curve by a constant dose of about 8 Gy.

Tumour cell survival in vitro *following treatment* in vitro

Figure 3A shows survival curves for cells taken from an unirradiated experimental tumour, plated, and treated approximately 18 hours later. Cells were exposed in hypoxia to a single dose or two doses 24 hours apart (being kept in air between fractions) and in air to single doses. The lines through the points have been fitted by eye. The D_0 (oxic) was 0.80 Gy, the oxygen enhancement ratio was 3.0 and the extrapolation number was 17. The D_q to the survival curve for hypoxic cells was about 7.0 Gy. The two-fraction survival curve for cells exposed to a priming dose of 14 Gy and graded doses 24 hours later was parallel to the single dose curve for hypoxic cells and displaced from it by about 6.0 Gy.

Figure 3B shows similar curves for cells taken from a culture in logarithmic growth of the established *in vitro* tumour cell line and irradiated approximately 18 hours later. The irradiation conditions were the same as for the cells from the tumour. The D_0 (oxic) was 0.90 Gy, the oxygen enhancement ratio was 3.2 and the extrapolation number was about 18. The D_q to the curve for hypoxic cells was about 8.5 Gy.

The priming dose for the two-fraction experiment was 16 Gy in hypoxia. The resulting two-fraction survival curve (for an interval of 24 hours) was parallel to and displaced from the single dose curve by about 5 Gy, indicating possibly incomplete recovery from sublethal damage. (Cells exposed to a single dose of 16 Gy and plated 24 hours later had lower survival (6.9×10^{-2}) than those plated immediately (9.4×10^{-2}). If this is allowed for, the displacement was about 6.0 Gy).

The survival curves shown in Fig. 3 were the results of experiments on cells from a single tumour (Fig. 3A), or on cells from a single *in vitro* culture in logarithmic growth (Fig. 3B). The experiments were repeated, but for clarity the results are not shown. The results were not significantly different in the repeat experiments. In particular, the estimates of (D_2–D_1) were 5.8 Gy for cells from a tumour, and 5.2 Gy for cultured cells.

DISCUSSION

Using a single murine tumour system and different methods of assay we have shown that the ability of tumour cells to recover from sublethal radiation damage depends both on their environment at the time of irradiation and on the method of assay. Table II lists the values of (D_2–D_1) measured by the different methods and the different survival curve parameters. For the TCD_{50} assay the range in the estimate of (D_2–D_1) represents the 95% confidence limits. For the growth delay assay and for cells assayed *in vitro* following treatment *in vivo*, the ranges of values for (D_2–D_1) were obtained by drawing "envelope" curves through the data points and measuring the maximum and minimum values of (D_2–D_1) using these curves. This procedure probably maximizes the errors. In spite of this, cells left *in situ* after irradiation clearly had a greater capacity for recovery than those plated *in vitro* following treatment *in vivo* (Table II). While the ranges for (D_2–D_1) overlap for the growth delay and cell survival assays, the two probably gave different results because (D_2–D_1) was increasing in the regrowth assay at doses-per-fraction for which it had reached a constant value in the cell survival assay (see Figs. 1 and 3). This implies that cells left *in situ* could absorb sublethal damage at doses greater than 14 Gy, but cells subsequently plated *in vitro* could not. The observation that (D_2–D_1) was less than D_q for cells irradiated and assayed *in vitro* could indicate that under the conditions of the experiments there was incomplete recovery even at 24 hours. An alternative explanation is that at the time of the second dose the cells had moved into a more sensitive phase of the cell cycle, resulting in a reduced shoulder to the survival curve for those cells that had survived the first dose. Nevertheless, the measured D_q of 7 and 8.5 Gy to the survival curves for hypoxic cells *in vitro*, whether from tumours or cell cultures, were both less than the measured values of (D_2–D_1) (*i.e.* estimates of D_q) for cells left *in situ* (Table II).

The processes involved in recovery from sublethal damage might be expected to be complete in the time interval of 24 hours between doses used in the present experiments. The observation that the repair increment was different for cells left *in situ* or plated after the second dose, implies that in the WHFIB tumour either recovery involves processes

TABLE II

SURVIVAL AND RECOVERY PARAMETERS DETERMINED FROM THE DIFFERENT ASSAYS. THE VALUES FOR (D_2–D_1) ARE FOR CELLS THAT WERE HYPOXIC AT THE TIME OF IRRADIATION. ALL DOSES ARE IN GRAYS.

Assay		D_0 (hypoxic)	D_q (hypoxic)	OER	D_2–D_1(24h)
Growth delay		—	—	—	13 (9–18)
TCD_{50}		—	—	—	14.7 (12.6–16.8)
Cell survival *in vitro* after treatment in *vivo*		4.0	3.0	—	8.0 (6.6–11.4)
Treated and assayed *in vitro*	Cells from tumours	2.4	7.0	3.0	6.0
	Cultured cells	2.9	8.5	3.2	6.0

TABLE III

IN SITU ASSAYS FOR $(D_2–D_1)$ FOR CLAMPED TUMOURS

Tumour	Histology	T_D(Days)	$D_2–D_1$ (24h) Gy	$(D_2–D_1)/2·7$	Reference
RIB$_5$	Undifferentiated fibrosarcoma	1	10.0	3.7	Field *et al.*, 1968
Bone Sarc. 'A'	Undifferentiated osteosarcoma	1.5	5.0	1.9	Denekamp and Stewart, 1978
MT	Anaplastic tumour	1.7	18.6	6.9	Sheldon (personal communication)
Squamous Ca. 'D'	Anaplastic tumour	2	14.0	5.2	Hill and Fowler, 1977
'Fibrosarcoma'	Moderately differentiated fibrosarcoma	2.7	10.0	3.7	Denekamp and Stewart, 1978
WHFIB	Anaplastic tissue culture adapted fibrosarcoma	3–4	14.0	5.2	—
Ca. 'NT'	Mod. differentiated adenocarcinoma	3	7.0	2.6	Denekamp and Harris, 1976
'BS2'	Anaplastic tumour	3.5	8.5	3.2	Denekamp and Harris, 1976
C3H	Mod. diff. mammary Ca.	—	6.2	2.3	Suit and Wette, 1966
C3H	Mod. diff. mammary Ca.	—	15 (6h)	5.6	Suit and Urano, 1969
C3H	Mod. diff. mammary Ca.	6	9.0 (6h)	3.3	Howes, 1969
C3H	Mod. diff. mammary Ca.	6	12.9	4.8	Fowler *et al.*, 1975
Carcinoma 'Rh'	Mod. diff. adenocarcinoma	7–12	11.5	4.3	Denekamp and Stewart, 1978
Sarcoma 'S'	Well diff. fibrosarcoma	7	0	0	Denekamp and Stewart, 1978

occurring after the second dose, which are affected by the post-irradiation conditions, or that there are qualitative differences in the types of damage expressed *in vivo* and *in vitro* (McNally, 1972b). The results also imply that measurements of the ability of tumour cells to recover from sublethal damage which involve removal of the cells from their normal environment may underestimate their ability to recover when left *in situ*. Whether or not tumours show less recovery from sublethal damage than normal tissues may not, therefore, be determined by *in vitro* assays.

In 1972, Phillips reviewed the available data on recovery in normal tissues and tumours and concluded that "tumours in both mixed acute and chronically hypoxic and entirely chronically hypoxic states show reduced recovery compared to skin, intestine and, in some cases, lung" (Phillips, 1972). While this is true for some tumours, it may not be correct as a generalization for all tumours (Withers, 1970). Typical dose-recovery values $(D_2–D_1)$ for these normal tissues ranged from 3.4 to 8.0 Gy for oxic cells depending upon the particular tissue (Phillips, 1972). In view of our observations that *in vitro* assay may be misleading, we have tabulated in Table III data on tumours from the literature based only on *in situ* assays, *i.e.* regrowth delay and tumour control probability. In all cases, tumours were clamped at the time of irradiation, to avoid problems of reoxygenation. The values of $(D_2–D_1)$ listed in Table III represent the maximum values that could be estimated from the published data. In order to compare the recovery values with those for normal tissues, they have been divided by an assumed oxygen enhancement ratio of 2.7. The tumour-volume doubling times have been included. Comparing the "oxic" values for $(D_2–D_1)$ with those for normal tissues, six out of fourteen are lower. The other eight give an average $(D_2–D_1)$ of 4.9 Gy, well within the range for normal tissues.

These results were obtained with tumours clamped at the time of irradiation so that the response of normally well-oxygenated cells was being measured. If chronically hypoxic cells are less able to recover than oxic ones this could result in tumours showing less recovery than normal tissues. Severe hypoxia between fractions is known to reduce the capacity of cultured cells to recover from sublethal damage (Littbrand and Revesz, 1969; Hall *et al.*, 1974; Koch *et al.*, 1973). In solid tumours two measurements on chronically hypoxic cells have implied a reduced capacity for recovery (Suit and Urano, 1969; Shipley *et al.*, 1975), while a third did not (McNally, 1972a). In the experiments of Shipley *et al.* (1975) and McNally (1972a), tumours were removed after treatment and single cell suspensions prepared. As the present results indicate, this may result in an underestimate of the capacity for recovery whether by chronically or acutely hypoxic cells. Hill and Bush (1977) concluded that chronically hypoxic tumour cells have a reduced capacity for absorbing damage as sublethal (reduced shoulder to the survival curve), but they, too, prepared single cell suspensions for their assay.

In the WHFIB tumour the majority of the cells appear normally to be hypoxic since clamping tumours or killing the animals before irradiation did not significantly increase survival relative to that for cells from unclamped tumours (McNally *et al.*, 1978). Consequently, in the present experiments, even though clamps were used, chronically hypoxic cells probably determined the response. While the extrapolation number to the survival curve for cells from irradiated tumours was less than that for cells *in vitro* (Figs. 3 and 4), the ability of the cells to recover was greater, particularly when they were left *in situ*. There is no evidence of recovery from potentially lethal damage in this tumour which could otherwise explain the greater recovery seen *in vivo* (McNally, unpublished).

In summary, differences in the responses of normal tissues and tumours to fractionated radiotherapy will only reflect differences in recovery from sublethal damage if the chronically hypoxic cells dominate the response of the tumour and show reduced recovery. However, the present results on the WHFIB fibrosarcoma have shown that measurements of tumour-cell survival and, in particular, of the ability of tumour cells to recover from sublethal damage, depend critically on the method of assay. Assays which involve removal of cells from their normal environment after irradiation may underestimate their true capacity for recovery, whether they are well-oxygenated or chronically hypoxic. There may be other differences between tumours and normal tissues, for instance in the magnitude of the initial slope to the survival curve (Denekamp and Stewart, 1978), which could lead to a therapeutic advantage from fractionation.

ACKNOWLEDGMENTS

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Book reviews

Clinical Nuclear Cardiology. By Robert W. Parkey, Frederick J. Bonte, L. Maximilian Buja and James T. Willerson, pp. 328 + index, 1979 (Appleton-Century-Crofts/Prentice/Hall International, Hertfordshire) £20·80
ISBN 0–8385–1146–5.

Several books have been published with a title like this but none can yet be considered satisfactory. Sadly, for all its merits, this new book still only gives a partially satisfactory account of nuclear cardiology in 1979. It has many good points. It is handy, well-written, well produced with good illustrations and lavish references. There are plenty of good line drawings and tables. It covers almost all aspects of nuclear cardiology, one exception being those techniques which do not use a gamma camera, such as Wagner's "nuclear stethoscope". Perhaps at the moment this is not a major fault. More seriously there is nothing on congenital heart disease or shunts.

What then is wrong? The trouble with the book is that of balance. The relative emphasis on the various techniques in no way reflects the interest or potential which they seem to possess at the moment. The book has over 330 pages. Introduction, physics and instrumentation, and radiopharmaceuticals take up 87 pages and these are very good. There are several small chapters on minor aspects, myocardial blood flow (18 pages), myocardial perfusion by intra-coronary particles (13 pages), "static" blood pool scanning (11 pages), and tomography (6 pages). But compared with these, thallium myocardial perfusion imaging is dealt with in 17 pages. Dynamic blood-pool imaging, both first pass and ECG gated imaging, is only accorded 19 pages. The great bulk of the book is a comprehensive study of myocardial infarct imaging, mainly with Tc-pyrophosphate. This is the main concern of nearly 150 pages.

Though individually the chapters are excellent, this is a distorted view of nuclear cardiology. In Europe at least, infarct imaging has not established itself as a major activity. Thallium imaging and blood pool imaging are the main directions of interest. If this book had dealt with these topics with the thoroughness with which it treats infarct imaging, then it would be sure of a place on the bookshelf of every cardiologist and nuclear medicine specialist working in the field. As it is, it can only be recommended as an introduction to the subject of its title, as an aid in teaching and as a source of references. And of course as a comprehensive text if you should be interested in Tc-pyrophosphate infarct scanning.

R. F. JEWKES.

Soft Tissues of the Extremities (*A Radiologic Study of Rheumatic Disease*). By W. J. Weston and D. G. Palmer, pp. xii + 128, 1978 (Berlin, Springer-Verlag), DM68/$34.00.
ISBN 3–540–90259–7

This book, part of a series of Comprehensive Manuals in Radiology produced by this publishing house, basically represents a distillate of the first author's many publications and great experience in this field. There are 128 pages divided into eight chapters on a regional anatomical basis. The print is clear and easily readable and the 171 illustrations are largely of high quality. The accompanying line drawings are excellent. A full bibliography is offered at the end of each chapter and the authors do not hesitate to commend classical articles to the reader who is in search of a more detailed description. The layout is generous, often with just over half a page being utilized. Typographical errors are few.

The book is intended to improve awareness of the soft tissue changes associated with rheumatoid disease. It does not attempt to correlate the prognostic or therapeutic significance of the described features. Differential diagnosis is scanty. Many soft tissue structures are described and illustrated by virtue of alterations in soft tissue density or the disturbance of fat planes. Proof of anatomical relationships is offered by many elegant post-mortem contrast medium studies. The illustrations would have benefited from more explicit labelling of the accompanying line drawings. The authors describe basic techniques of arthrography and tenography but do so insufficiently for those requiring to practice arthrography beyond the skills necessary for the investigation of rheumatoid disease. The reviewer would join the quoted references in this volume who dispute that arthrographic opacification of lymphatics is pathognomonic of rheumatoid disease.

The authors succeed in their principal aim in provoking the reader to examine with more care the soft tissue structures so easily ignored on "bone and joint films" and to ponder upon the relevant anatomy. They offer useful lists of signs and beautiful illustrations. The volume is small and the script short. It offers an anatomical study for those working towards the First Part of the Radiological Fellowship and a quickly assimilated lesson for those reading for Final Fellowship. It will no doubt be appreciated by those in training in allied disciplines, particularly rheumatology. It should be present on the shelves of all training departments and libraries.

IAIN WATT.

1979, *British Journal of Radiology*, *52*, 650–656

Evidence for acutely hypoxic cells in mouse tumours, and a possible mechanism of reoxygenation

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ABSTRACT

The proportion of viable hypoxic cells in EMT6/St/lu tumours assayed 18 and 24 hours after a dose of misonidazole (1.2 mg/g), which killed 80–90% of the tumour cells, was reduced from 20% in the controls to 7% in the misonidazole treated mice. In other experiments, the radiation cell-survival curve of the RIF-1 tumour was assayed in both intradermal and intramuscular sites under both air-breathing and acutely hypoxic conditions. The slope of the survival curve of the intramuscular tumours irradiated under air-breathing conditions was significantly steeper than that of the same tumours growing intradermally (D_0 values of 187 rad vs. 357 rad), or when the tumours were irradiated in either site under acutely hypoxic conditions ($D_0 = 375$ rad).

Both of these experimental observations are examined in the light of data from other sources, notably from the radiation response of hypoxic cells in spheroids and from observations made from tumours implanted between close, parallel mica sheets ("sandwich" tumours). It is concluded that these results, taken together with the other data, suggest that rodent tumours contain acutely hypoxic cells, as well as the classically described chronically hypoxic cells.

It is argued further that, if (as appears to be the case) acutely hypoxic cells are produced by intermittent opening and closing of tumour blood vessels, then this process would provide a simple explanation for the rapid reoxygenation seen in several mouse tumours. Finally, it is pointed out that a consequence of the presence of acutely hypoxic cells in tumours is that they would largely frustrate attempts to radiosensitize tumours using either respiratory inhibitors or high pressure oxygen, or agents designed to selectively kill hypoxic tumour cells, since both of these methods would deal only with the chronically hypoxic cells.

We noted recently that EMT6 tumours contain hypoxic cells even after the killing of 80 to 90% of the tumour cells with high doses of misonidazole, and this led us to suggest that these tumours might contain acutely as well as chronically* hypoxic cells (Brown *et al.*, 1978). Since such a conclusion, if true for tumours in general, would have important implications for experimental and clinical work, evidence is presented here which has bearing on this question. Two sets of previously unpublished data are presented: the first, details of the experiment mentioned above, in which the hypoxic fraction was determined in EMT6 tumours after extensive cytotoxicity produced by misonidazole: the second, evidence that there are hypoxic cells of different radiosensitivities in RIF-1 tumours depending on the site of implantation of the tumour. These latter experiments were performed to test the hypothesis that if the temporary (partial or total) closure of blood vessels in tumours is the mechanism by which acute hypoxia occurs (as is suggested by the data of Reinhold *et al.*, 1977 and Intaglietta *et al.*, 1977), then the same tumour implanted in different sites of the mouse would have different types of blood supply and hence might have different proportions of acutely and chronically hypoxic cells. Such an expectation of different tumour blood supplies for tumours in different tissues is based on the finding that the total blood flow to a tumour is limited by the normal arterial supply to that region in the absence of the tumour (Intaglietta *et al.*, 1977).

Finally, additional evidence, drawn from the work of others, is presented which has relevance to the question of whether tumours contain acutely as well as chronically hypoxic cells. Should this turn out to be the case, and if it is a result of a temporary closure of blood vessels as is suggested, then a rather simple explanation for the rapid reoxygenation found in several mouse tumours (Kallman, 1972; 1974) suggests itself.

MATERIALS AND METHODS

The tumours in this investigation were the EMT6/St/lu† tumour transplanted into BALB/c, and the RIF-1 tumour, a non-immunogenic radiation induced sarcoma, recently developed at Stanford for *in vivo-in vitro* assay, transplanted into C3H mice.

A description of the procedures for transplantation, irradiation and assay of the viability of the EMT6/St/lu tumour cells has been published previously (Brown, 1975). Briefly, however, the EMT6 tumour was implanted intradermally in the under non-anaesthetized conditions when it reached a diameter of 6 mm. Immediately after irradiation the tumours were removed, minced and a single cell suspension prepared using an enzyme "cocktail" of 0.02% collagenase, 0.05% pronase and 0.02% DNAase. Cell viability was assayed by plating appropriate dilutions of the tumour cells into polystyrene Petri dishes and counting colonies 13 days later. The details of handling, irradiation, preparation of single cell suspensions and viability assay of the RIF-1 tumour were identical to those for the EMT6/St/lu tumour.

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*"Chronically hypoxic" cells are defined in the present context as cells which have been hypoxic for a considerable time (more than one hour), are likely to be close to areas of necrosis and will die if not "rescued" in some way. It is envisaged that they are present beyond the diffusion distance of oxygen from viable blood vessels. "Acutely hypoxic" cells are defined as those which have become hypoxic in the very near past (less than one hour), and are not necessarily far from blood vessels.

†Because of the wide variation among different lines of EMT6 tumours in different laboratories, it was decided at a recent meeting of EMT6 users (May 14, 1978, Toronto) to adopt a laboratory specific designation for sublines. The EMT6/St/lu is the "lung passaged" line of the EMT6 tumour at Stanford (as opposed to the "intradermally passaged" line), and is the same as that discussed in previous publications (Brown, 1975; 1977).

The misonidazole used was dissolved immediately prior to use in physiological saline at a concentration of 20 mg/ml, so that dose a of 1 mg/g was injected i.p. in a volume of 1.25 ml for a 25 g mouse.

Results

Hypoxic fraction in EMT6 tumours following misonidazole-induced cytotoxicity

Figure 1 shows drawings from histological sections of EMT6 tumours both before and 24 hours after a high dose of misonidazole (1.2 mg/g).

At 24 hours after misonidazole injection there is little or no free nitroimidazole in the tumours, and consequently any hypoxic cells remaining have a characteristically resistant radiation cell survival curve. Thus it is possible to determine the hypoxic fraction in tumours several hours after injection of misonidazole by the usual method of determining the separation of the radiation cell-survival curves obtained from animals breathing air, or dead (*i.e.*, with the tumour cells hypoxic), at the time of irradiation. This was done both 18 and 24 hours after a single dose of 1.2 mg/g of misonidazole to EMT6 tumour-bearing mice. The two experiments gave similar parallel lines, and the pooled data (Table I) gave a value for the hypoxic fraction in saline injected mice of 19% (95% confidence intervals 11% to 31%) and in misonidazole-treated mice of 7% (4%–12%). Thus, there were significantly fewer hypoxic cells in misonidazole-treated tumours than in control tumours ($0.01 < p < 0.02$). Nevertheless, there still remained large numbers of hypoxic cells in the drug-treated tumours.

Radiation sensitivity of intradermal and intramuscular RIF-1 tumours

2×10^5 RIF-1 cells were injected intradermally into the flank tissue of C3H mice (a site with limited blood flow), and three days later a similar inoculum was injected into the muscle of the right hind leg

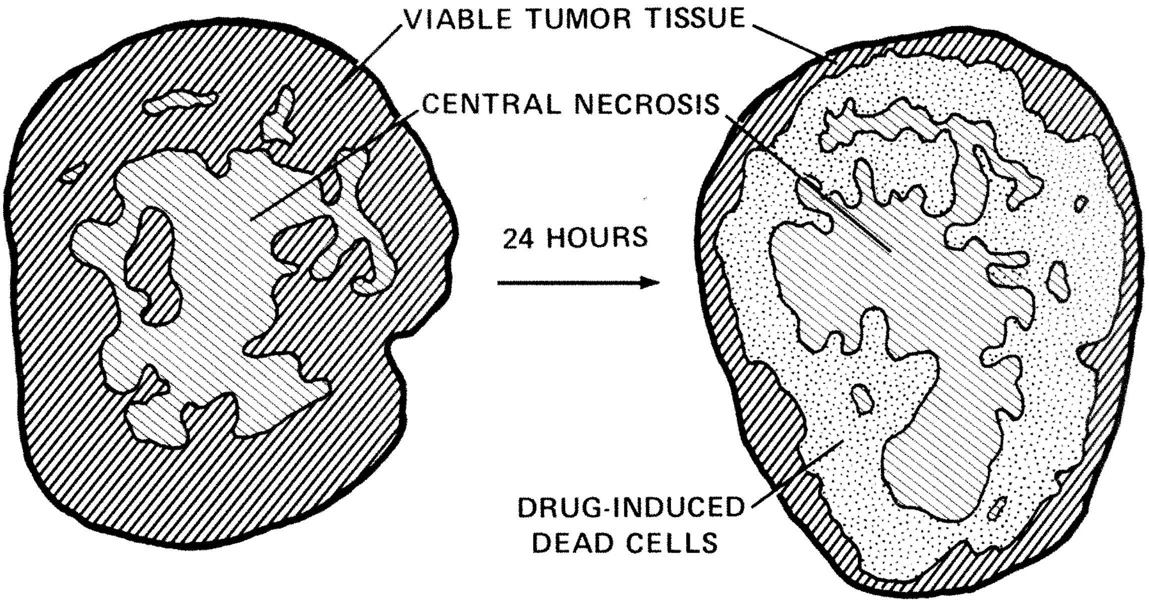

Fig. 1.

Drawings of 6–7 mm diameter EMT6 tumours before and 24 hours after an injection of 1.2 mg/g of misonidazole into tumour-bearing mice. The viable tumour tissue is reduced from 1–2 mm in thickness to approximately 0.2 mm thick (previously published in Brown *et al.*, 1978).

TABLE I

THE "HYPOXIC FRACTION" IN EMT6 TUMOURS 18 AND 24 HOURS AFTER PRETREATMENT WITH MISONIDAZOLE

Radiation dose to tumours (rad)	Ratio of air/N_2 surviving fractions of paired points			
	Experiment I (18 hr before irradiation)		Experiment 2 (24 hr before irradiation)	
	Saline	Misonidazole	Saline	Misonidazole
1.000	0.22	0.10	0.35	0.13
1.333	0.18	0·02	0.40	0.07
1.667	0.09	0.07	0.24	0.04
2.000	0.20	0.12	0.07	0.11
Mean (95% C.I.)	0.16 (0.08–0.32)	0.07 (0.02–0.22)	0.22 (0.06–0.77)	0.07 (0.03–0·20)
Probability of diff.	$0.05 < P < 0.10$		$0.01 < P < 0.05$	
Mean of expts 1 & 2	Saline: 0.19 (0.11–0.31) Misonidazole: 0.07 (0.04–0.12)	$0.01 < P < 0.02$		

TABLE II

D_0 VALUES OBTAINED FOR THE RIF-1 TUMOUR IRRADIATED UNDER DIFFERENT CONDITIONS

Expt. no.	Site of implantation	Conditions of irradiation	D_0 values (95% confidence interval)	Prob. of difference of D_0 values*
3	Leg muscle	Anoxic Air-breathing	343 (260–504) 177 (125–298)	$P = 0·02$
	Flank intradermal	Anoxic Air-breathing†	344 (263–497) 339 (191–1520)	N.S.
4	Leg muscle	Anoxic Air-breathing	390 (295–573) 198 (156–269)	$P < 0·01$
5	Flank Intradermal	Anoxic Air-breathing†	450 (367–583) 424 (132–2621)	N.S.
3,4,5 combined	Leg & Flank Leg muscle Flank intradermal	Anoxic Air-breathing Air-breathing†	375 (333–428) 187 (160–223) 357 (260–564)	$P < 0·01$

*Based on a two-tailed test of significance using Student's distribution of the pooled error variance of the data around the best-fitting least-squares regression lines.

†From inspection of the data, the resistant "tail" becomes evident above 1500 rad. Therefore, only data at 1667 rad and above are included in the analysis.

(a region with a large blood flow). Eight days after the intramuscular injection the tumours had reached the same weights in legs and flanks, and the mice were irradiated with various doses to the whole body either under air-breathing, non-anaesthetized conditions, or having been killed prior to exposure, and the tumours assayed for cell survival immediately after irradiation. The data obtained from this and two repeat experiments are shown in Fig. 2 and Table II.

It can be seen that the slopes of the cell-survival curves for the tumours irradiated in dead mice are the same irrespective of site of implantation. However, the slope of the survival curve of cells in the tumours implanted in the leg muscle in air-breathing mice is significantly greater ($p < 0.01$) than

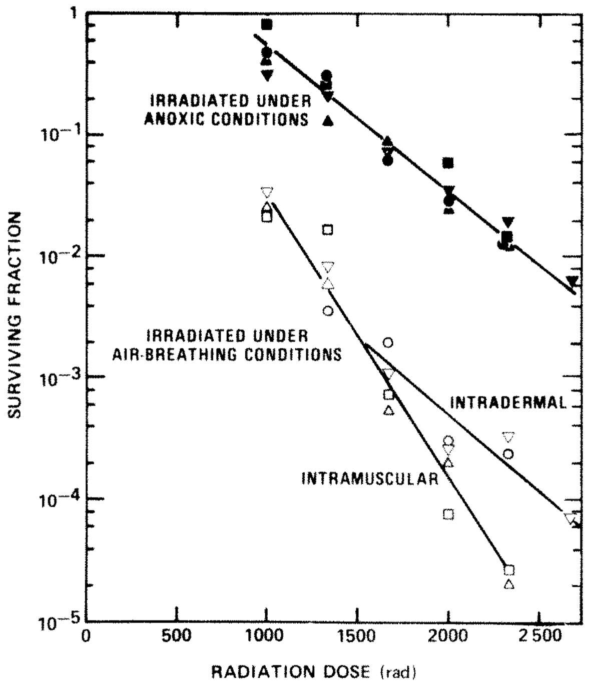

FIG. 2.

Radiation cell-survival curves of the RIF-1 tumour implanted either intramuscularly (■▲□△) or intradermally (●▼○▽). The mice were not anaesthetized for irradiation, and the similar symbols for irradiation under air-breathing and anoxic conditions show data obtained in the same experiment.

that obtained for tumours irradiated under acutely hypoxic conditions (*i.e.*, in dead mice). On the other hand, it appears that the slope of the terminal portion of the cell-survival curve for the intradermally inoculated tumours is the same under both air-breathing and anoxic conditions of irradiation, and significantly different ($p < 0.01$) from the slope of the curve for intramuscular tumours irradiated in air.

DISCUSSION

The experimental data presented show that viable hypoxic cells are present in the peripheral rim of EMT6/St/lu tumours after extensive killing of the central cells with misonidazole, and that the radiosensitivity of the hypoxic cells in RIF-1 tumours differs if the tumours are implanted intradermally or intramuscularly. As discussed below, both of these observations can be interpreted on the basis that there are acutely as well as chronically hypoxic cells in these tumours. In order to discuss the implication of these observations for tumour oxygenation, other evidence both from spheroids and from microscopic observations in "sandwich" tumours is presented. Thus, I have listed below the evidence supporting the concept that rodent tumours contain acutely hypoxic cells, as well as the classically described chronically hypoxic cells.

Evidence for acutely hypoxic cells in tumours

1. In the experiments in which 1.2 mg/g of misonidazole was given to mice bearing EMT6 tumours, the number of clonogenic cells extracted from the tumours 24 hours after injection was approximately 20% of that of the controls (18% in one experiment, 25% in the other). This has been interpreted as cytotoxicity of the misonidazole to both oxygenated and hypoxic cells (Brown, 1977) Furthermore, as illustrated in Fig. 1, it appears from histological examination that the remaining viable cells were present only in the peripheral rim of the tumours (Brown, 1977). Since there were no areas of necrosis in these peripheral regions, it would appear that these hypoxic cells are present in the well vascularized rim of the tumours and hence would not be expected to be chronically hypoxic unless a significant proportion of such chronically hypoxic cells in tumours do, in fact, exist in regions remote from necrosis (this seems unlikely but cannot be rejected). Also, the possibility cannot be excluded that these were chronically hypoxic cells which developed in the tumour during the previous 12 hours or so before the irradiation exposures. However, the lack of any necrotic areas near this peripheral rim makes this possibility seem unlikely.

Thus, this observation suggests that hypoxic cells are present in the outer, and (presumably) well vascularized rim of EMT6 tumours, and are not confined solely to regions close to necrotic areas. Further, these cells were not killed by a dose of misonidazole which kills 80–90% of the tumour cells, which suggests that they were not hypoxic at the time when the misonidazole, or its toxic metabolite(s), were present in the tumour. Both observations, then, suggest that these are acutely hypoxic cells.

2. Spheroids which contain a necrotic center are a good example of a tumour cell population *in vitro* which contains chronically hypoxic cells. The radiation survival curve of such spheroids is biphasic, with a resistant "tail" which can be manipulated by changing the oxygenation conditions of the medium. However, it has been generally observed that the D_0 of this resistant tail is not greater than that of the well oxygenated spheroid cells by the full OER of 2.5–3.0 (Franko, 1976; Durand and Biaglow, 1977; Franko and Sutherland, 1979). For example, from measurements made from the published curves in

the paper of Durand and Biaglow (1977), an "OER" for 592 μm diameter spheroids (D_0 for resistant tail/D_0 for dissociated cells) of 1.83 is obtained compared with the OER of 2.90 for the same cells in monolayer culture. According to the work of Franko and Sutherland (1979), the D_0 of the chronically hypoxic cells in V79 spheroids is a factor of 1.2 to 2.3 times that of the oxygenated cells depending on the growth conditions, whereas the full OER of 2.8 is obtained when the spheroids are made acutely hypoxic (Franko, 1976; Franko and Sutherland, 1979). If these results can be extrapolated to solid tumours, it follows that chronically hypoxic cells (*i.e.*, cells adjacent to necrotic areas) in solid tumours might be more radiosensitive than the tumour cells made acutely hypoxic. Yet, invariably, the survival curves of tumour cells irradiated in air-breathing mice are parallel to those obtained from the same tumours made acutely hypoxic by killing the mice prior to irradiation (Tannock, 1972). This means that, if tumours contain chronically hypoxic cells of intermediate radiosensitivity, they must also contain acutely hypoxic cells, otherwise the survival curves of the cells irradiated in air-breathing mice would not be parallel to those obtained from dead mice. It should be noted that the intermediate radiosensitivity of the chronically hypoxic cells may be a result either of their age distribution, of their nutritional state, or of an intermediate level of oxygenation.

3. In painstaking observations of tumours implanted between close, parallel windows ("sandwich" tumours) Yamaura and Matsuzawa (1979) have observed that those tumours which regrew following high doses of irradiation did so from foci in the peripheral, well vascularized regions of the tumours rather than from areas close to necrotic regions. Thus, the most resistant cells of these tumours appeared to be in the well vascularized regions and not close to the necrotic areas or around tumour cords where traditionally one would expect to find chronically hypoxic cells. A reasonable explanation of this finding is that the cells from which the tumours regrew were acutely hypoxic, presumably as a result of a temporary occlusion of their oxygen supply.

4. Again with "sandwich" tumours, it has been observed that blood flow may slow down or cease temporarily in individual blood vessels, and that this produces fluctuations from full oxygenation to hypoxia in well vascularized regions of the tumours (Reinhold *et al* 1977; Intaglietta *et al.*, 1977). According to Reinhold *et al.*, (1977) such fluctuations occurred in 10–20% of the tumour regions (of 100 μ diameter) investigated. This, then, is suggested as the mechanism by which temporary, acute hypoxia might occur in otherwise well vascularized regions of tumours.

5. The evidence presented in 1–4 above suggests firstly, that tumours contain both acutely hypoxic and chronically hypoxic cells, and secondly, that the chronically hypoxic cells are of intermediate radiosensitivity between acutely hypoxic and fully oxygenated cells. The experiment described above to examine the radiosensitivity of the hypoxic cells in RIF-1 tumours implanted in two different sites was done to see whether tumours with very different blood supplies might show a detectable difference in their types of hypoxic cells.

It was found (Fig. 2 and Table II) that the radiosensitivity of the hypoxic cells in the intramuscular tumours was significantly greater than both that of the hypoxic cells in the flank-implanted tumours and that of either group of cells made acutely hypoxic.

Since it would be expected that the blood supply of the tumours growing in the leg muscle would be more vigorous (and possibly less liable to temporary cessation) than that of tumours growing intradermally in the flank, one might expect that acutely hypoxic cells would not occur in these muscle-implanted tumours. Thus, they should only contain chronically hypoxic cells, and if the data obtained from spheroids is applicable, these hypoxic cells should be more sensitive than the acutely hypoxic cells growing in the intradermally implanted tumours. This appears to be the case. We have also obtained confirmation that these cells of intermediate radioresistance in the intramuscular tumours are indeed hypoxic since they can be radiosensitized with misonidazole, and also the D_0 of these cells grown *in vitro* is 133 rad (Brown *et al.* 1979), substantially lower than the D_0 of about 185 rad given in Table II. It would appear from the extrapolation number of the survival curve of the intramuscular tumours that 25–100% of the cells in these tumours are of this intermediate radiosensitivity.

It should be noted that there is an alternative explanation for the lower D_0 of the cells of the muscle-implanted tumours: it could be a consequence, not of their chronic hypoxic state (as postulated above), but of their fluctuating between full oxygenation and acute hypoxia. This would be consistent with the periodicity of 1–3 minutes found for the fluctuations in oxygenation in "sandwich" tumours (Reinhold *et al.*, 1977; Intaglietta *et al.*, 1977) and with an irradiation time of 11–12 minutes for 2000 rad but not consistent with the spheroid and other data presented. Also, for this explanation based on fluctuating hypoxia to fit these data, one would need to postulate a different periodicity for the intramuscular and intradermal tumours.

However, since both explanations involve postulating the presence of acutely hypoxic cells in tumours, the distinction between the two explanations can perhaps be left unresolved.

Although each of the above pieces of evidence is not conclusive in itself, taken together they provide evidence that there may be two types of hypoxic cells within mouse tumours: chronically hypoxic cells which mainly occur adjacent to areas of necrosis and at a given distance from viable blood vessels (Thomlinson and Gray, 1955; Tannock, 1968; Thomlinson, 1977), and acutely hypoxic cells which are produced by the temporary cessation of blood flow in individual vessels within tumours.

A suggested mechanism for reoxygenation

If tumours do, in fact, contain both acutely hypoxic cells and chronically hypoxic cells, and if, as is suggested from the data from the spheroid and "sandwich" tumour experiments, the chronically hypoxic cells are more radiosensitive than the acutely hypoxic cells, one would expect that following a large dose of irradiation (more than 1000 rad) the majority of the cells surviving would be these acutely hypoxic cells. Thus, a mechanism for the rapid reoxygenation which has been observed in many experimental tumours (Kallman, 1972; 1974) immediately suggests itself. Reoxygenation would be the result of the normal return of the blood supply (and hence oxygen) to these temporarily static vessels (assuming that radiation does not interfere with the normal stopping and starting of blood flow). Thus, although previously open blood vessels would close rendering the cells around them acutely hypoxic, very few of these cells would be viable (since they were fully oxygenated at the time of irradiation). Hence, the proportion of viable cells in the tumour which were hypoxic would fall (*i.e.*, the tumour would reoxygenate). Since Kallman (1974) has observed virtually full reoxygenation in the KHT and EMT6 sarcomas and in the KHJJ carcinoma within an hour after a conditioning dose of 1000 rad, this time scale indicates fluctuations in oxygenation with a periodicity of less than one hour.

Such a mechanism for reoxygenation of the acutely hypoxic cells does not exclude the possibility that chronically hypoxic cells may also become reoxygenated, perhaps by mechanisms previously suggested (Kallman, 1972).

Consequences of tumours containing acutely hypoxic cells

The consequence of tumours containing acutely hypoxic cells is that their presence will frustrate those attempts to eliminate hypoxic cells in tumours which are based either on specific killing of chronically hypoxic cells, or on attempts to increase the diffusion distance of oxygen from blood vessels. In the former category is the use of the cytotoxic action of electron affinic radiosensitizers to chronically hypoxic cells (Adams, 1977); in the latter group are respiratory inhibitors which have been suggested as adjuncts in radiotherapy because of their ability to increase the diffusion of oxygen to poorly oxygenated regions (Durand and Biaglow, 1977). Also in the latter category is the use of high pressure oxygen, and it is perhaps significant that in single-dose experiments high pressure oxygen has not been found to greatly modify the response of some animal tumours (Suit and Maeda, 1967) (although other explanations, such as oxygen induced vasoconstriction, could account for these failures). However, it should be noted that the use of electron-affinic agents to sensitize hypoxic cells to radiation is not frustrated by the presence of acutely hypoxic cells, since these agents appear to be uniformly distributed in tumours because they profoundly modify the response of tumours to single doses of irradiation.

Finally, a consequence of the presence in tumours of acutely hypoxic cells and the more radiosensitive chronically hypoxic cells adjacent to necrotic areas, is that these chronically hypoxic cells may not be relevant to the radiation response of tumours either because these cells are more radiosensitive than the acutely hypoxic cells, or because they are destined to die if left *in situ*. Indeed it could be that the tumour cord model of blood vessels, viable tumour tissue, hypoxic viable cells and necrosis (Thomlinson and Gray, 1955; Tannock, 1968; Thomlinson, 1977) which has so dominated radiobiological thinking for the past 20 years has, in fact, been leading us to false conclusions.

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Book review

Practical Aspects of Electron Beam Treatment Planning. Edited by C. G. Orton and F. Bagne, pp. 109, 1978, (American Institute of Physics, for American Association of Physicists in Medicine), $10.00.
ISBN 0–88318–247–5

This book, the second in a series of Medical Physics Monographs published for the American Association of Physicists in Medicine (AAPM), is the proceedings of a symposium held in 1977 on the practical aspects of using electron beams clinically. The contents of the 109 pages provide a useful practical guide to the problems associated with electron beam therapy, particularly with reference to electrons in the energy range 5–45 MeV although one chapter is devoted to the clinical and physical problems of using electrons with energy less than 5 MeV.

The first three of the six chapters of the book deal with dosimetry problems, the importance of obtaining accurate positional data and the problems in using electrons in radiotherapy and how corrections can be made for inhomogeneities. These chapters contain much previously published information and little new material, but the contents do provide the reader with good background data. Two chapters are then devoted to algorithms which have been used for computer calculations of electron dose distributions. The review covers the three main methods adopted, namely the empirical, semi-empirical and analytical algorithms, thereby providing the reader with a useful synopsis of the work already done in this field. Although the writer does state he is not prepared to say which method is best, the final choice must rest with the local user. Following the chapter on the use of low energy electrons, the book concludes with a report on the discussions which resulted from these papers.

This monograph provides a good summary of the work done to date and a basic guide to the practical aspects of electron beams in treatment planning, and the total of 131 references in the book should provide readers with a useful starting point for additional reading. At its moderate cost, this book will be a useful acquisition to any physics department involved in using electrons in the treatment of malignant disease.

T. J. Godden.

1979, *British Journal of Radiology*, *52*, 657–662

The effect of local hyperthermia on the small intestine of the mouse

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ABSTRACT

Small loops of mouse jejunum were exteriorized and heated by immersion in a bath of Krebs-Ringer salt solution. Crypts were lost in the heated regions with a half-time of approximately six hours and reached a steady level of damage by 10–16 hours. There was no recovery in crypt number for one week after hyperthermia. Using a 24 hour assay, crypt survival curves were obtained using various heating times in the temperature range 37.5°C–44.5°C. These curves were qualitatively similar to those resulting from radiation damage, showing a shoulder followed by exponential killing. As the temperature was increased, progressive changes in shape of the curves indicated a proportional inhibition of accumulation of sublethal heat damage combined with increased rate of expression of lethal damage. Over the temperature range 42.3°C–44.5°C, a linear relationship was found between the rate of crypt loss and the reciprocal of the absolute temperature. An activation energy of 600±70 kJ mole^{-1} was calculated using the Arrhenius equation. In this temperature range, doubling the heating time had the same effect as increasing the temperature by 1°C. At temperatures below about 42.3°C, the tissue became relatively less sensitive to increasing the treatment time.

The present use of hyperthermia in the clinical treatment of cancer is based on several features of hyperthermal cell killing which, if correctly administered, may give an increased differential between the response of normal and tumour tissues (for recent reviews see Overgaard, 1978; Field, 1978). Heat may be applied either alone or in combination with chemotherapy or radiotherapy. Potentiation of the normal response to drugs or radiation is observed, with or without any observable cell killing effect of the heat alone.

A favourable therapeutic approach might be to combine direct heat damage with one or even both of the enhanced modalities. In each case the treatment to be given will be limited by the responses of normal tissues. There is evidence from both *in vitro* and *in vivo* work to suggest that different cell types have considerably different sensitivities to hyperthermia (Westra and Dewey, 1971; Harris, 1967; Thrall *et al.*, 1976; Hand *et al.*, 1978). It therefore becomes important to study in detail the effects of heat on those tissues at risk in any treatment.

It has been possible with normal tissues *in situ* to distinguish, both qualitatively and temporally, two different types of tissue injury resulting from direct heat damage or thermal enhancement of X-ray damage (Morris *et al.*, 1977; Law *et al.* 1978; Field, 1978). In the intestine, mild hyperthermia enhances the normal radiation response (Hume and Field, 1978; Merino *et al.*, 1978). The present paper describes a study of the direct effect of heat on the small intestine of the mouse, the reaction being of a different nature and occurring earlier than the radiation response.

METHODS

Female CFLP mice (10–12 weeks old) were anaesthetized by intraperitoneal injection of sodium pentobarbitone at 0.07 mg/g body weight. A section of the jejunum, approximately 10 cm long, was exteriorized through a small incision. The jejunal loop was marked in the middle with a small stitch and heated by immersion in a small Perspex bath of Krebs-Ringer solution. This bath was partially submerged in a larger, water-filled bath, the latter being thermostatically controlled. A small propellor in the Krebs bath ensured adequate stirring and the temperature could be maintained to within ±0.1°C of that required. During heating the mice were given additional anaesthetic subcutaneously. Intestinal temperatures were monitored in several mice using copper/constantan thermocouples (100μm diameter) and digital thermometers with 0.1°C resolution. The thermocouples were inserted through the jejunal wall either "near to" (within 0.5 mm) or diametrically opposite to the mesenteric blood vessels and sutured in position.

After heating, the exteriorized loop of the intestine was replaced in the intraperitoneal cavity and the wound closed with stitches. After recovering from anaesthesia, the animals were active and ate normally. At various times after treatment, animals were sacrificed by cervical vertebral dislocation. The treated portion of the intestine was fixed in Bouin's solution and 5 μm thick transverse sections were prepared. The effects of heating were assayed by counting the number of crypts per mm of jejunal circumference either adjacent to or diametrically opposite to the mesenteric blood vessels. Typical regions over which counts were made are shown in

Fig. 1B. The mice which had been used for temperature measurements were not included in the histological analysis. Normal counts were approximately 20 crypts per mm. The musculature of the small intestine remained intact and the circumference of the histological sections was not significantly altered by the heat treatment. For example, mean values of circumference, with standard errors from 10 sections, were 8.6±0.3 from control mice, 9.2±0.5 from mice heated at 43°C for 30 minutes and 8.7±0.3 from mice heated at 44°C for 30 minutes, sampled 24 hours after treatment.

RESULTS

Figure 1A illustrates the asymmetric effect of heating an exteriorized loop of mouse jejunum for 30 minutes in a Krebs bath at 43.5°C. For comparison, Fig. 1B is a section from a mouse which was treated in the same way except that the bath temperature was 37.5°C. In the heated intestine most damage is seen in regions diametrically opposite to the mesenteric blood vessel. This observation has also been made, in a similar preparation, by Merino *et al.*, 1978. It has been accounted for by temperature differentials across the exteriorized intestine which have been attributed to the cooling effect of blood flow (Hume *et al.*, 1979; Hand *et al.*, 1979a). Using a 30 minutes heat treatment, temperature differences of approximately 1°C between regions "near to" and "far from" the mesentery were recorded by the above authors. The number of surviving crypts at these positions at two different temperatures is also illustrated from the present work in Fig. 2. In contrast, however, if the intestine were heated by lower body immersion rather than by exteriorization, no thermal gradients were detected (Hume and Field, 1978).

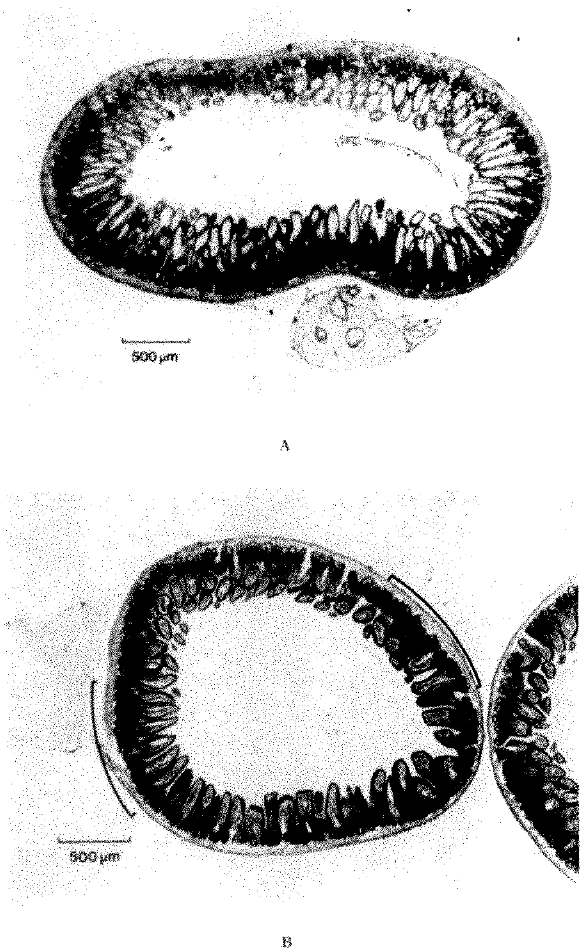

FIG. 1.

Transverse sections of mouse jejunum stained with haematoxylin and eosin. Mice were sacrificed 24 hours after a heat treatment of (A) 43.5°C for 30 minutes or (B) 37.5°C for 30 minutes.

Figure 2 shows the rapid expression of heat injury in the intestine, as assayed by crypt loss. The half-time of loss was approximately 6 hours. Following severe hyperthermia (44.0°C for 30 minutes), crypts were totally destroyed in the heated portion of the intestine after about 24 hours, but only on the side

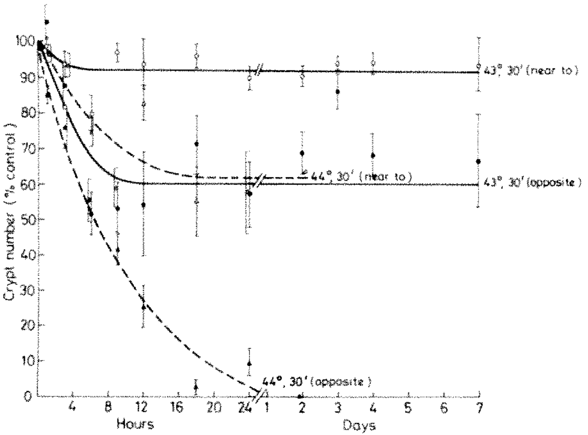

FIG. 2.

Time course of crypt loss per mm length of jejunal circumference, following two hyperthermal treatments. Counts were made either adjacent to or diametrically opposite to mesenteric blood vessels. Unheated mice were used as the control. The majority of points are from six mice. Standard errors are shown.

○—○ 43.0°C for 30 min, sampled "adjacent to".
●—● 43.0°C for 30 min, sampled "opposite".
△--△ 44.0°C for 30 min, sampled "adjacent to".
▲--▲ 44.0°C for 30 min, sampled "opposite".

opposite to the mesentery. After moderate hyperthermia, crypt numbers decreased for about 16 hours. Thereafter there was little evidence of recovery or repopulation for up to one week after treatment. Crypt loss appeared to be an "all or none" effect; those which were degenerating had no dividing cells whereas those which survived showed relatively little damage and had a normal mitotic index. Sections sampled soon after treatment showed oedema, with apparent loss of surface epithelium and marked villous damage, dependent on the severity of the hyperthermal treatment. This is shown in Fig. 3. Because loss of villi preceded loss of crypts, with "rapid recovery" of intact villi between 6 and 12 hours after treatment, it is possible that the observed histological pattern was an artefact, resulting from loss of tissue during sampling and fixation due to transient fragility, rather than a measure of depopulation followed by repopulation.

Crypt assay was normally carried out 24 hours after treatment. Figure 4 shows the effect of temperature and length of heating time on crypt damage assayed at this time, either opposite (Fig. 4A) or adjacent to (4B) mesenteric blood vessels. Bath temperatures are given and heating times are taken from the time of immersion to the time of removal from the Krebs bath. Regions opposite blood vessels reached equilibrium temperatures, which were typically 0.1°C below bath temperature, within about 20 seconds of immersion. Data obtained for some similar temperatures, *e.g.*, 43.8°C and 44.0°C, have been combined if the curves for the pooled data were not significantly different from each other. This probably reflects the inability to stabilize intestinal (and Krebs bath) temperatures to closer than 0.2°C. Regions adjacent to the mesentery showed greater variation in temperature and scatter in the biological data than those opposite to the mesentery as might be expected from the temperature dependence on blood flow. Since the local temperature was not known for each treatment, being dependent on distance from the major mesenteric blood vessels and the length of heating time, analysis of the "near to" data is not presented.

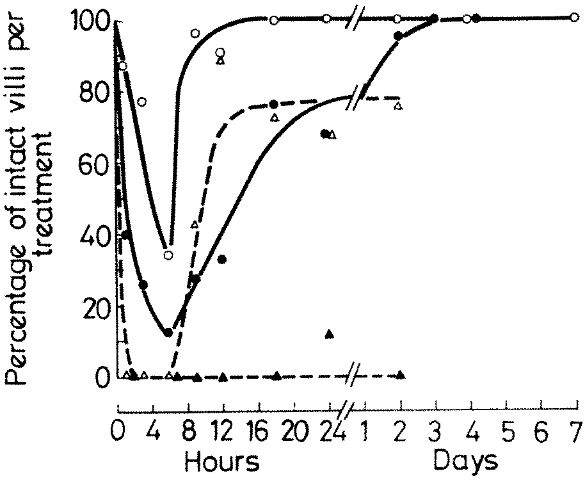

FIG. 3.

Increased intestinal fragility, as indicated by loss of villous structure, at early times after hyperthermia. Two temperatures were used and the proportion of jejunal sections showing loss of surface epithelium and marked villous damage counted at various times after treatment. Judgements were made for regions either "adjacent to" or "opposite" mesenteric blood vessels, for an average of 45 sections per treatment.
○—○ 44.0°C for 30 min, sampled "adjacent to".
●—● 43.0°C for 30 min, sampled "opposite".
△--△ 44.0°C for 30 min, sampled "adjacent to".
▲--▲ 44.0°C for 30 min, sampled "opposite".

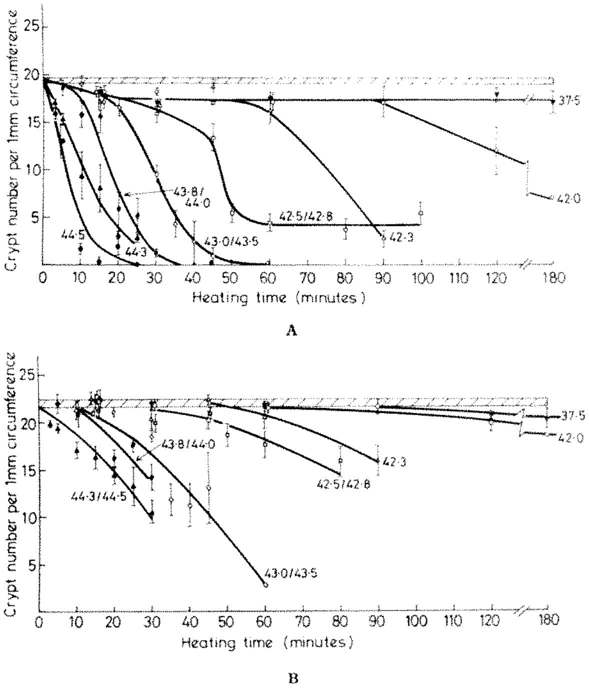

FIG. 4.

Effect of temperature and heating time on crypt number per mm length of jejunal circumference, assayed 24 hours after treatment. Bath temperatures are given. Counts were made either opposite (A) or adjacent to (B) mesenteric blood vessels. The hatched region on each graph represents the standard error about the mean value from unheated mice. The data points are means, with standard error bars, from an average of six mice.

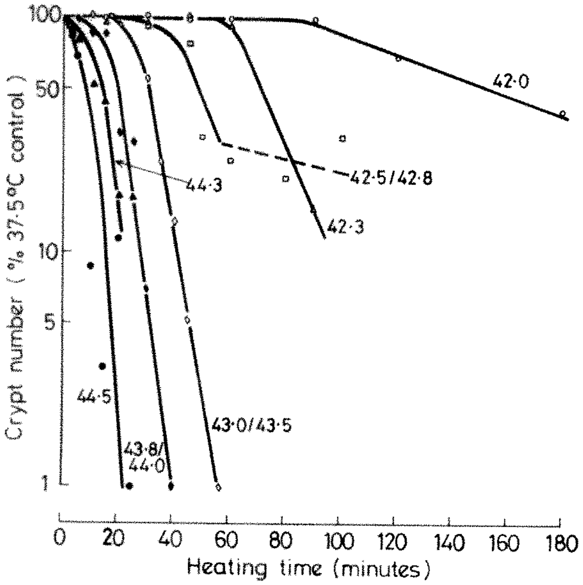

FIG. 5.

Crypt survival curves, assayed 24 hours after treatment. The points are calculated from Fig. 4A, as a percentage of the appropriate 37.5°C control. The exponential regions of the curves were fitted by regression analysis, excepting those at 42.3°C, 44.3°C and 44.5°C.

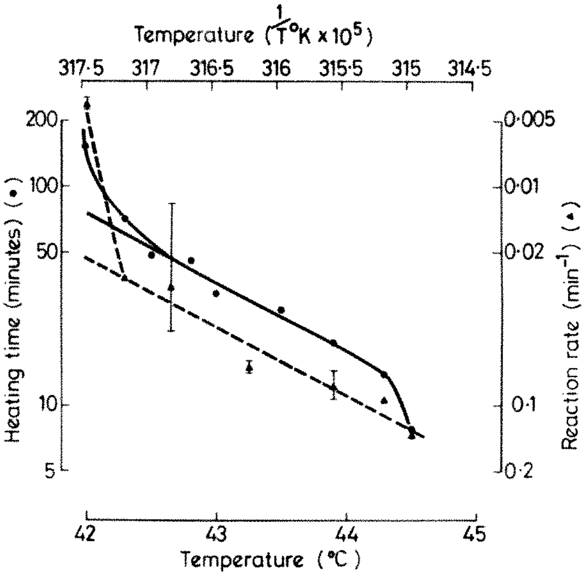

FIG. 6.

Correlations between (1) heating time and temperature for 50% damage ●—●, and (2) temperature and tissue sensitivity to increasing heating time, ▲--▲. Data for the 50% level of damage were taken from Fig. 5. Rates of crypt destruction with increasing heating time per temperature were calculated from the best fit exponential slopes in Fig. 5.

TABLE I

CRYPT SURVIVAL CURVE PARAMETERS

Temperature (°C)	"D$_0$" (min)	"D$_q$" (min)
42.0	103	85
42.3	16	60
42.5/42.8	15.5	37.5
43.0/43.5	7	26
43.8/44.0	5.5	16
44.3	5	11
44.5	3.5	7.5

Crypt survival data from regions opposite mesenteric blood vessels are presented in the semi-logarithm plots of Fig. 5. They are expressed as a percentage of the 37.5°C control in order to compensate for the small reduction in crypts due to the exteriorization technique, as seen in Fig. 4A. If the curves are considered to be analogous to survival curves obtained after ionizing radiation, then values of "D$_0$" (the reciprocal of the slope of the curve) and "D$_q$" (the intercept with the abscissa) can be measured. These are given in Table I. As the treatment temperature is increased from 42.3°C to 44.5°C, the heating time equivalent to "D$_q$" is decreased and the rate of crypt destruction (indicated by "D$_0$") is increased. Following heating at lower temperatures, *e.g.*, 42.0°C, the thermal damage is less than that which might be predicted by extrapolation from the higher temperature data. This is seen more clearly in Fig. 6.

The solid and dashed lines in Fig. 6 are Arrhenius-type plots taken from the data in Fig. 5. The solid line is an isoeffect curve, correlating heating time with temperature to produce a 50% loss in crypt number at 24 hours after treatment. Within the temperature range 42.5°C–44.3°C the curve approximates to a straight line, a rise in temperature of 1°C being equivalent to halving the heating time. Above this temperature there appears to be a rapid increase in the heat susceptibility of the tissue, which is manifest by a decreased shoulder. At lower temperatures the tissue appears to be less affected by heat.

The dashed line in Fig. 6 is a correlation between reaction rates (or inactivation rates), calculated from the slopes of the exponential portions of the crypt survival curves, with the reciprocal of the absolute temperature. The uncertainties in the points are standard deviations in the slopes. For temperatures below about 42.3°C there is a change in slope of the Arrhenius plot. For temperatures above 42.3°C, activation energy was calculated from the slope of the line calculated by least squares fit. A value of 600 ± 70 kJ mole^{-1} was obtained.

DISCUSSION

We have previously reported the thermal enhancement of the effects of X rays on the small intestine when heating was achieved by immersion of the lower body for 60 minutes, using temperatures up to 42.1°C (Hume and Field, 1978). In this temperature range, there was no observable effect of heat alone and the assay used was the same as that for the irradiation end-point, *i.e.*, survival of the mice at five days. The effect of heat was to reduce the shoulder of the X-ray survival curve without affecting its slope. Similar results have been obtained for crypt survival at four days following lower-body hyperthermia (Hume, unpublished data) and for local heating of exteriorized intestine (Merino *et al.*, 1978).

As seen in Fig. 2, the effect of heating to higher temperatures resulted in a much earlier expression of tissue response than that following ionizing radiation. After X-irradiation, cell division is delayed but total crypt degeneration does not occur until 2–3 days after treatment accompanied by a reduction in size and number of villi (Quastler, 1956). Following hyperthermia, the intestine immediately becomes locally oedematous and crypt loss is complete by 10–16 hours. A further qualitative difference between the two types of response is that for one week after hyperthermia there is no recovery in crypt number whereas, following X rays damaged crypts with only one clonogenic survivor can regenerate so that 3½–4 days after a sub-lethal dose there is an increase in crypt count (Withers and Elkind, 1970).

In the exteriorized intestine the effect of heat is asymmetrical; gradients of thermal damage are obtained which can be correlated with local temperature and distance from major mesenteric blood vessels (Hume *et al.*, 1979). Although the temperature differentials are sufficient to explain the results in terms of cooling by blood flow, the possibility that local hypoxia and/or increased acidity in regions distant from major blood vessels sensitizes the tissue to hyperthermia cannot be excluded (Dewey *et al.*, 1977; Overgaard, 1977; Morris *et al.*, 1977). These factors might be exacerbated by the exteriorization technique and could explain the slight reduction in crypt number which is observed in regions opposite to blood vessels following exteriorization times longer than about 20 minutes (see 37.5°C curve in Fig 4A).

Logarithmic plots of surviving fraction of crypts, 24 hours after treatment, as a function of heating time for each temperature (Fig. 5), gave curves which were qualitatively similar to those which have been frequently described for X-irradiation of the intestine (*e.g.* Withers and Elkind, 1970), thermal enhancement of radiation damage in the intestine (Hume and Field, 1978; Merino *et al.*, 1978) and also for hyperthermal killing of mammalian cells *in vitro* (Westra and Dewey, 1971). As the temperature was increased from about 42.3°C to 44.5°C, the capacity to accumulate sublethal heat damage was reduced and the expression of lethal damage increased. This can be compared with the potentiating effect of mild hyperthermia on radiation damage, where only the shoulder of the crypt survival curve was significantly altered.

As judged by the threshold hyperthermal treatment required to cause cellular death in other normal tissues in rodents, intestine appears to be more sensitive to heat than some tissues, *e.g.*, skin (Law *et al.*, 1977) and tails of baby rats (Morris *et al*, 1977), but less sensitive than testis (Hand *et al.*, 1979b).

In the temperature range given above, the relationship between heating time and temperature required to produce a given level of damage, 50% reduction in crypt number (Fig. 6), was similar to that which has been reported for a variety of endpoints based on normal tissue damage (review by Field, 1978), tumour cure (review by Overgaard, 1978) and mammalian cells *in vitro* (Suit and Schwayder, 1974; Dewey *et al.*, 1977), *i.e.* a 1°C rise in temperature is about equivalent to a 50% reduction in heating time.

An Arrhenius-type plot of the reaction rate as a function of the reciprocal of the absolute temperature gave an activation energy of 600 ± 70 kJ mole^{-1}. This was calculated from the slope, using the Arrhenius equation:

$$K = A \exp\left(\frac{-E}{RT}\right)$$

where E = activation energy, T = absolute temperature, K = rate constant and R = molar gas constant (A is approximately constant for a reaction over a small temperature range). This value for activation energy is very similar to that found in other tissues *in vivo* and *in vitro* and falls within the range reported for several enzymes and proteins (Johnson *et al.*, 1954), suggesting that denaturation of a critical protein or proteins may be the lethal event in heat damage (Westra and Dewey, 1971). It also indicates that normal and tumour cells and cells *in vitro* are killed by heat in a similar manner.

As can be seen from Fig. 6, there is a change in the slope of the Arrhenius plot at a temperature close to 42.3°C. Similar biphasic patterns have been reported for tumours (see Overgaard, 1978) and mammalian cells (Dewey *et al.*, 1977; Loshek *et al.*, 1977), with the change in slope occurring between 42°C and 43°C. This transition indicates either a change in activation energy, and thus a different mechanism of cell killing, or could reflect the development of thermal resistance over the longer heating times (Dewey *et al.*, 1977). With reference to the latter possibility, there is some evidence from the results presented that at intermediate temperatures, *e.g.* 42.5°C and 42.8°C, thermal resistance develops during treatment times longer than about 60 minutes. This is indicated by the flattening of the survival curve in Fig. 5.

A similar transition has been reported in the response of mouse splenic lysosomes to heating (Hume *et al.*, 1978a). Temperatures up to 42.3°C cause an increase in enzyme activity, whereas those above 42.5°C result in an increase in lysosomal membrane permeability. Induced thermal resistance has been observed in the latter response (Hume *et al.*, 1978b) but not the former, strongly implicating the role of a membrane in direct heat injury. It is thus possible that if thermal death is a result of denaturation of a critical cellular protein, its location may be in the lipoprotein membrane complex (Bowler *et al.*, 1973).

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Technical note

The choice of film for ultrasound imaging

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With the development of camera backs, both manually operated and automatic, which will take X-ray film, there has been increasing interest in the best choice of film for permanent recording of ultrasound images. X-ray film has the advantage that it reproduces the full range of grey tones displayed on the monitor and is also relatively cheap. In X-ray departments it can be processed in conventional automatic processors, although smaller dedicated processors are also now available for the isolated ultrasound department.

Several types of X-ray film designed for ultrasound work are on the market and there was a review of some of these by Copland *et al.* (1978).

Recently a new film (SP 440X) has been developed by Ilford Limited for use with ultrasound imaging. This has been compared with the other films currently in use for ultrasound imaging in the radiology department of The London Hospital. The results were obtained by exposing the film in a 25 × 20 cm (10 × 8 in.) camera back with a Shackman camera to a blank television screen, the brightness of which was measured with a photometer. The films were developed in a Du Pont automatic processor.

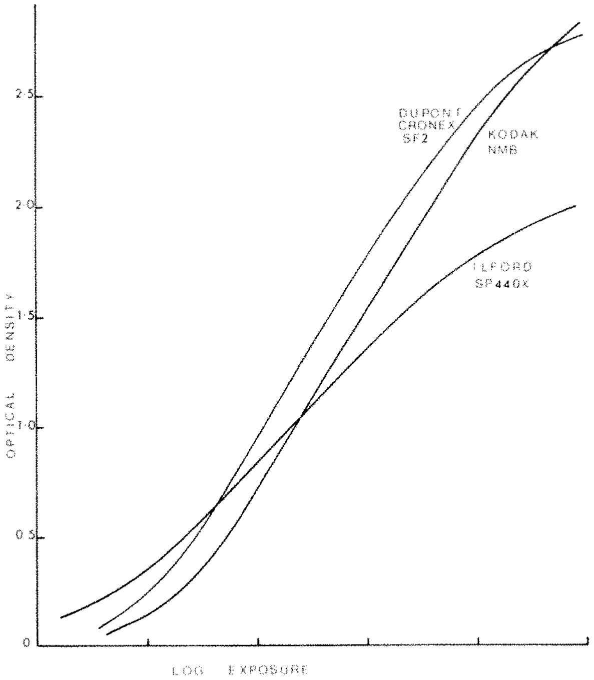

FIG. 1.
Characteristic response curves for Du Pont, Ilford and Kodak films.

It can be seen (Fig. 1) that the SP 440X has a lower gamma and lower density range than the other two films. The density range is quite large enough for routine use and the lower gamma appears to have the advantage of making the contrast setting of the TV monitor easy to adjust. The relative film speeds and gammas are shown in Table I.

It should be noted that, providing a film has a wide enough density range (by which is meant the range of densities corresponding to the straight line part of the curve), the gamma and latitude are largely irrelevant. The gamma and latitude can effectively be accommodated by means of the brightness and contrast controls of the monitor. By measuring the brightness with a photometer and adjusting the contrast and brightness controls, the tonal range can be made to fall within the straight line part of the response curve. Under normal viewing conditions a density of about 1.5 is the largest that seems to be acceptable, though this of course is subject to personal preference. The

TABLE I
RELATIVE FILM SPEED AND GAMMA FOR THE FILMS TESTED

Film	Speed	Gamma
Kodak NMB	1.0	1.5
Ilford SP 440X	1.1	1.0
Du Pont Cronex SF2	1.5	1.5

useful part of the response curve of a film is then the straight line part up to a density of approximately 1.5. Allowance may be made for the drift of brightness which is usually associated with scan converters by leaving a margin between each end of the tonal range of the monitor and the limits of the useful part of the response curve.

Thus, the choice of film may be made on general criteria such as cost and individual preference, and the monitor adjusted to suit the particular characteristics of the film.

Acknowledgments

We should like to thank Mr. R. Ruddick of the Medical Photography Department of The London Hospital for his help and advice, and Messrs. Ilford Ltd. for the supply of their film.

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Book review

Modern Radiation Oncology—Classic Literature and Current Management. 1st ed., Edited by Harvey A. Gilbert, and A. Robert Kagan, pp. xxi+712, illus., 1978 (Harper and Row, Inc., Maryland), $42.50.
ISBN 0-06-140910-3.

This book contains a representative cross section of articles written by recognized authorities in particular fields of radiation oncology. Perhaps the most useful way to convey the nature of the work is to list the classic articles and their authors.

Radiation therapy in the management of neoplasms of the central nervous system, with a special note in regard to children: twenty years' experience, 1939–1958, *J. Bouchard*, and *C. B. Peirce*; Treatment of nonfunctioning chromophobe adenomas of the pituitary, *G. E. Sheline*; Conventional radiation therapy in acromegaly, *Ann M. Lawrence*, *S. M. Pinsky* and *Ira D. Foldfine*; Craniopharyngiomas, *S. Kramer*, *W. McKissock* and *J. P. Concannon*; The value of radiation therapy in the management of glioma of the optic nerves and chiasm, *J. M. Taveras*, *L. A. Mount* and *E. H. Wood*; The treatment and prognosis of medulloblastoma in children, *H. J. G. Bloom*, *E. N. K. Wallace* and *J. M. Henk*; Radiation treatment of cancer of the pharynx: with special reference to telecobalt therapy, *M. Lederman* and *R. F. Mould*; Cancer of the nasopharynx, *C. C. Wang*, *J. B. Little* and *M. D. Schulz*; Oral cancer: a twenty-five year study, *C. L. Ash*; Malignant disease of the paranasal sinuses and nasal cavity, *M. L. M. Boone*, *T. S. Harle*, *H. W. Higholt* and *G. H. Fletcher*; Comparison of medium voltage and supervoltage roentgen therapy in the treatment of oropharynx cancers, *G. H. Fletcher*, *W. S. MacComb*, *P. M. Chau* and *W. G. Farnsley*; Cancer of the larynx I, *M. Lederman*; Roentgentherapy in cancer of the hypopharynx, *F. Baclesse*; Cancer of the laryngopharynx, *V. M. Dalley*; Hypopharyngeal carcinoma, *T. Inoue* and *Y. Shigematsu*; Clinical trials in malignant disease 3, *R. Paterson* and *Marion H. Russell*; The role of radiation therapy in esophageal center, *V. A. Marcial*, *J. M. Tomé*, *J. Ubiñas*, *A. Bosch* and *J. N. Correa*; Combined therapy: irradiation and surgery in the treatment of bronchogenic carcinoma, *F. G. Bloedorn*, *R. A. Cowley*, *C. A. Cuccia* and *R. Mercado, Jr.*; Role of intensive radiotherapy in the management of Hodgkin's disease, *H. S. Kaplan*; The contribution of radiation therapy in the control of early lymphomas, *M. Vera Peters*; Radiotherapy in carcinoma of the bladder: possible complications and their prevention, *F. G. Bloedorn*, *J. D. Young*, *C. A. Cuccia*, *R. Mercado, Jr.* and *M. J. Wizenberg*; Testis, *M. Friedman*; Carcinoma of prostate, *B. S. Barringer*; Cancer of the uterine cervix, *G. H. Fletcher*; Evolution of radiotherapeutic techniques, *L. W. Brady*, *G. C. Lewis, Jr.*, *J. Antoniades*, *S. Prasasvinichai*, *R. J. Torpie*, *S. O. Asbell*, *J. R. Glassburn*, *D. Schatanoff* and *T. MacMurray*; The changing prognosis and treatment in cancer of the ovary, *E. W. Munnell*; The management of soft tissue sarcomas in adults, *R. D. Linberg*, *G. H. Fletcher* and *R. G. Martin*; Ewing's sarcoma, *R. D. T. Jenkin*; Chemotherapy in the treatment of leukemia and Wilms' tumor, *S. Farber*; Radiotherapy in the treatment of orbital tumors, *M. Lederman*.

The main coverage of the book is thus revealed but it is far from simply a collection of important papers. There is a commentary after each section which provides much additional information and also annotated bibliographies dealing with major topics. The volume is well indexed and this provides the reader with easy access to the material which is presented in a very readable way. It is a high quality publication which should withstand the heavy demands likely to be placed on it by individual readers and departmental libraries.

For the busy clinician striving to keep up to date as well as for the student of higher examinations, it is to be strongly recommended.

Brendan Hale.

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Case reports

Sub-diaphragmatic gas in a case of acute pancreatitis

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Bacterial gas formation in the region of the pancreas is an uncommon X-ray finding in acute pancreatitis (Weens and Walker 1964). The gas formation may occur in the pancreas itself (emphysematous pancreatitis) or surrounding tissues, or pancreatitis may result in a gas forming abscess in the lesser sac. These conditions may be difficult to differentiate radiologically and similarly intestinal air may cause confusion (Renert *et al.*, 1973).

The incidence of abscess following acute pancreatitis has been reported to range from 1·5% (Steedman *et al.*, 1967) to 4·5% (Altemeier and Alexander, 1963).

An unusual case of necrotizing pancreatitis is described, which developed some of the above features, with sub-diaphragmatic gas, which aroused suspicion of a perforated viscus. Later, a pneumomediastinum appeared.

CASE HISTORY

A 58-year old male presented with right hypochondral pain of sudden onset which had been present for four hours and accompanied by profuse vomiting. There was no previous history of dyspepsia, abdominal pain or fat intolerance. He drank alcohol rarely.

On examination he was unwell, sweating and had epigastric tenderness. Chest X-ray and erect and supine straight abdomen X-rays showed no abnormality. Biochemical investigation revealed: serum amylase 7,600 somogyi units; white cell count 26,000/mm^3; serum calcium 2·26m mol/l; blood sugar 9·0m mol/l.

A diagnosis of acute pancreatitis was made. Conservative treatment was instituted with intravenous fluid, Trasylol and glucagon but his condition deteriorated and by the third day subcutaneous discolouration due to retroperitoneal haemorrhage appeared in his flanks (Grey-Turner's sign). The serum calcium dropped to 1·96m mol/l.

Straight abdomen X-rays showed free gas under both hemi-diaphragms (Fig.1) and the presence of diffuse mottled lucencies extending across the mid line indicating retroperitoneal gas (Figs. 2A and B). Gas was also visible in the lienorenal ligament, around the spleen medially and around the gallbladder. Small scattered fluid levels were present indicating an ileus. An associated perforated viscus was suspected.

At laparotomy a severe haemorrhagic pancreatitis was found with bloody free fluid in the peritoneum. On opening the lesser sac gas was heard escaping. There was no evidence of a perforation. Flank drains and a peritoneal dialysis catheter were inserted. Peritoneal swab and blood cultures grew Aerobacter aerogenes, a gas forming organism.

Following laparotomy the patient was treated with intravenous lincomycin and gentamicin, peritoneal lavage and intravenous fluids, but remained critically ill on the intensive care unit. After two days he developed a pneumomediastinum (Fig. 3) and patchy pneumonic consolidation appeared in both lungs. He died four days after the laparotomy.

Autopsy report

Acute necrotising pancreatitis, bronchopneumonia and pneumomediastinum. No gut perforation found.

DISCUSSION

There is a widely varying incidence of positive X-ray findings in investigated series of pancreatitis. This to some extent depends upon criteria for abnormal bowel distention due to ileus. However even in severe haemorrhagic pancreatitis, plain abdomen X-rays may be quite normal. In a series of Weens and Walker (1964) approximately two thirds of the cases of acute pancreatitis showed no significant abnormality.

Gas in the pancreas is an uncommon X-ray finding but when present is a pathognomonic sign of acute pancreatitis (Renert *et al.*, 1973). Enzymes are released into the surrounding tissues causing fat necrosis and digestion, and secondary bacterial invasion results in gas formation. The characteristic of retroperitoneal gas is mottled lucencies which may lie along fascial planes and on erect or decubitus films these gas collections show only limited mobility, which is a reliable distinction from intraperitoneal gas. These gaseous lucencies may extend across the mid line and down the flanks extraperitoneally in the anterior pararenal space (between the posterior parietal peritoneum and the renal fascia), but this is exceptional, as collections are normally confined to one side (Meyers 1974). In the case described gas was also present in the posterior pararenal space (between the posterior renal fascia and fascia transversalis). This compartment continues laterally as the properitoneal flank stripe, and superiorly as a thin subdiaphragmatic layer of fat. Extension of gas into the posterior

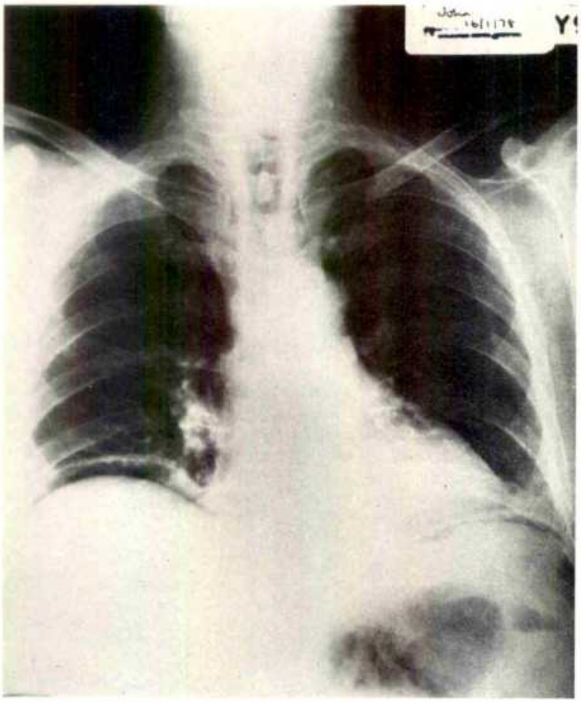

FIG. 1.
Erect chest X-ray showing gas under both hemidiaphragms. This film was taken at the same time as Fig. 2.

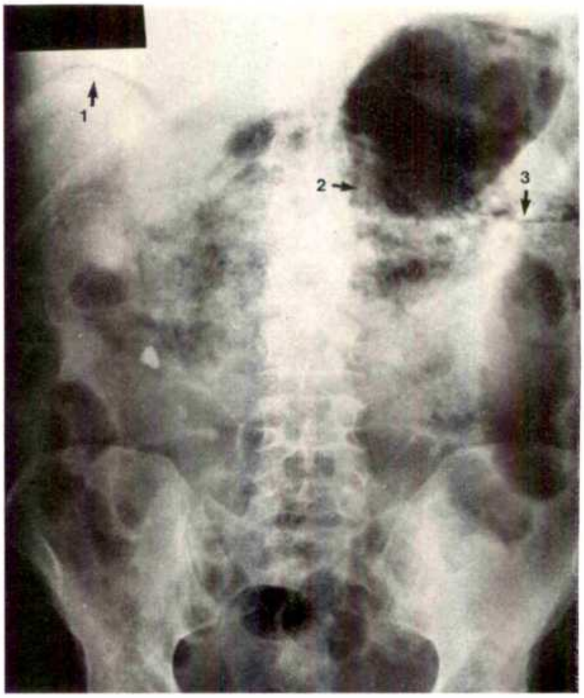

FIG. 2A.
Supine abdominal X-ray showing retroperitoneal gas in pancreatic region extending across mid-line. Gas is also shown (1) around the gall bladder, (2) in the left adrenal area, (3) around the spleen.

pararenal space is shown here by outlining the left adrenal gland, the medial contour of the posterior aspect of the spleen and the medial crus of the diaphragm. The gas immediately below the diaphragms is probably both extra and intraperitoneal.

Gas may ascend from the posterior pararenal space, as in this case, through the diaphragmatic hiati resulting in pneumomediastinum, but this is a most unusual finding in pancreatitis, which is previously unreported. However, it must be stated that the pneumomediastinum could possibly have resulted from positive pressure ventilation, or even the laparotomy, but this was thought unlikely in this case.

The usual respiratory complications are pleural effusion, diaphragmatic elevation, atelectasis and pulmonary oedema (Kaye 1968, Murphy *et al.*, 1977). Mediastinal extension of pancreatic pseudocysts is well described (Kaye 1968), but not pneumomediastinum.

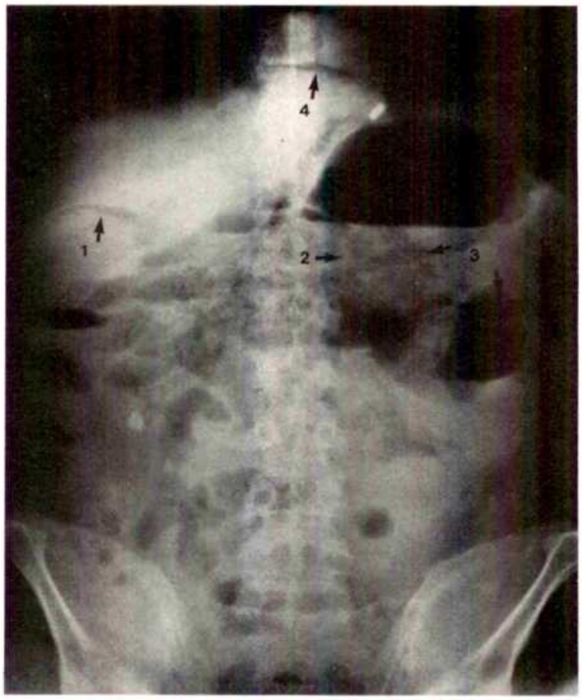

FIG. 2B.
Erect abdominal X-ray with similar numbered features to Fig. 2A. Also gas is shown under the medial part of the diaphragm (4).

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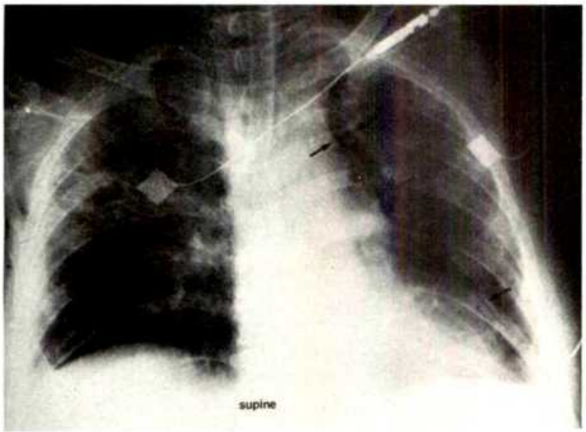

FIG. 3.

Penumomediastinum, also consolidation right upper lobe.

Pancreatic abscess (retroperitoneal abscess or abscess of the lesser sac) is probably the most serious complication of pancreatitis with severe post-operative complications after surgical drainage. In the series of Holden (1976) there were major post-operative complications in over 90% of cases, and mortality of 50%. Operative treatment must be aggressive and persistent, with extensive drainage. The usual development of necrotizing pancreatitis is from a haemorrhagic, to a gangrenous to a suppurative stage, all of which logically should be treated by surgical evacuation (Hubbard *et al.*, 1972). Similarly Grace and State (1976) have stated that the management for pancreatic abscess is early recognition and drainage. They had a higher success rate, with eight out of nine patients with primary abscess surviving.

The plain abdomen findings of the case described here show just how widespread the retroperitoneal and intraperitoneal extensions of pancreatitis may be and the complicated anatomical pathways along which infection may spread, including the route into the thorax. These extensions must be searched for and drained (Hubbard *et al.*, 1972).

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Diagnosis of a small acoustic neuroma by metrizamide computer-assisted cisternography

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CASE REPORT

A 28-year-old woman presented with a nine-month history of trigeminal neuralgia in the third division of the right fifth nerve. She had no clinical neurological deficit. X-rays showed widening of the right internal auditory meatus, and auditory testing revealed a lesion of the right eighth nerve. Conventional CT with intravenous contrast medium (50 ml Conray 420; *i.e.* 21 g of iodine) was negative (Fig. 1). A computer-assisted cisternogram (Fig. 2) performed after an injection of 8 ml of 170 mg I/ml metrizamide into the lumbar subarachnoid space (Hindmarsh and Greitz, 1977) showed a small right cerebello-pontine angle mass, which was confirmed by myodil meatography. At operation a 1.0 cm acoustic neuroma was removed with preservation of the facial nerve.

DISCUSSION

Hindmarsh and Greitz (1977) showed that the basal cisterns can be demonstrated by CT with positive contrast after a lumbar injection of metrizamide more clearly than on a conventional plain scan. Drayer and Rosenbaum (1976) Drayer *et al.* (1977 a, b and c) and Davis *et al.* (1977), have shown that this method is of value in diagnosing lesions at the base of the skull.

Conventional CT with intravenous contrast medium can show acoustic tumours greater than

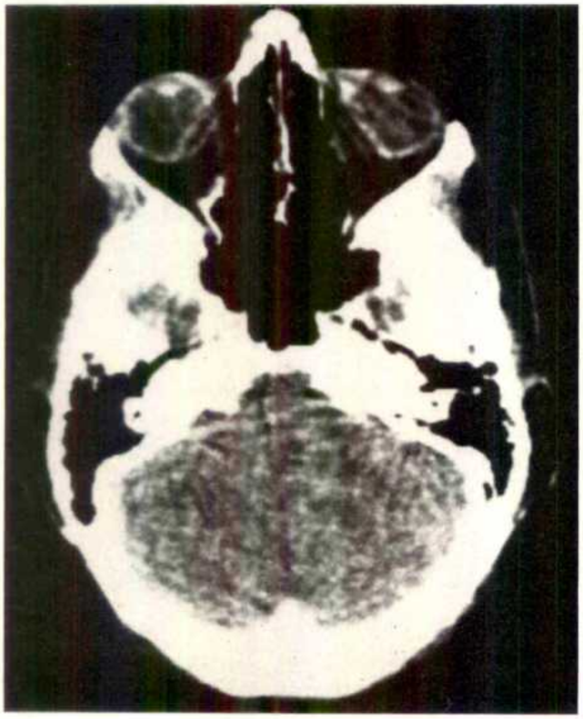

Fig. 1.

Right acoustic neuroma. Conventional CT scan with intravenous contrast medium is normal.

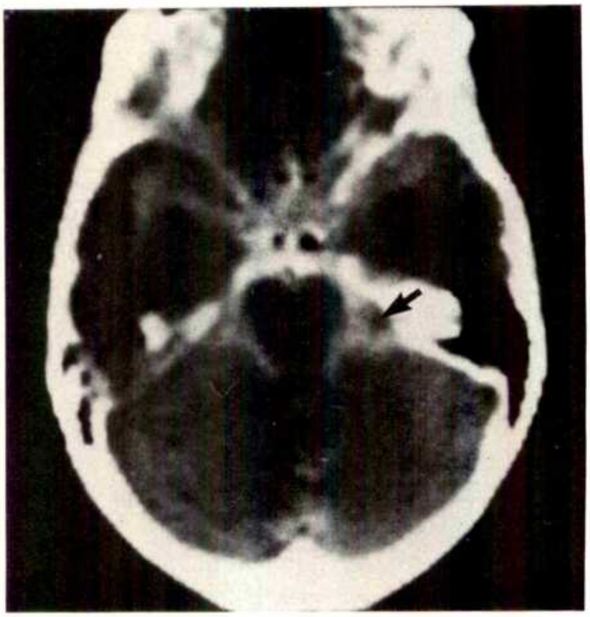

Fig. 2.

Metrizamide CT scan. A mass (arrow) is shown in the right cerebello-pontine angle.

2.5 cm in diameter (King and Ambrose, 1977; Kazner *et al.*, 1976; Davis *et al.*, 1977) but smaller tumours may not be revealed. Until recently many small acoustic tumours could only be diagnosed by myodil (Burrows, 1969) or air (Isherwood, 1972), cisternography. Metrizamide computer-assisted cisternography is a new development, which has some advantages.

With myodil studies adhesions may sometimes be mistaken for very small tumours (Burrows, 1969). Further, myodil itself may cause adhesions in the subarachnoid space and persistent globules of myodil may compromise subsequent tests.

Metrizamide computer-assisted cisternography is technically simple to perform and in contrast to air studies causes little distress to the patient. The contrast medium is absorbed in about 24 hours in otherwise normal cases.

These advantages suggest that metrizamide computer-assisted cisternography has an important place in the diagnosis of small basal tumours. We recognize that its limitations in the diagnosis of extremely small and intra-canalicular tumours have not been established.

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Occult cardiac metastasis and mitral reflux

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In malignant disease, cardiac metastases occur late (Jefferson and Rees, 1973), are usually right-sided (Lymburner, 1934) and have been reported as an often unsuspected post-mortem finding in 10% of cases (Heath, 1968). We describe a patient who presented with cardiovascular symptoms due to a left atrial metastasis which made subacute bacterial endocarditis or atrial myxoma seem likely diagnoses. These symptoms arose at a time when malignant disease was not suspected and the primary gastric carcinoma was clinically silent.

CASE REPORT

A 47-year-old housewife presented with a five-month history of lassitude, weight loss and shortness of breath. She had paroxysmal nocturnal dyspnoea on two occasions. On examination she appeared anaemic, had a persistent fever and a pan systolic murmur was audible over the apex. Investigations showed Hb 8.8 g; low iron and total iron binding capacity; plasma viscosity 2.12; albumen 2.7 g; globulin 4.2 g. The white cell count was normal. Reactive looking monocytes were noted in the bone marrow. Blood cultures were consistently negative. A chest radiograph revealed slight enlargement of the left atrium. A left ventriculogram showed gross mitral reflux (Fig. 1). Ultrasound examination of the heart did not reveal evidence of mitral stenosis or left atrial myxoma (Fig. 2). In spite of the negative blood cultures, subacute bacterial endocarditis was considered to be the most likely diagnosis. Intravenous penicillin in a dose of 20 mega units daily was given for a month. Review of the patient's clinical course and investigations drew attention to a previously noted but non-healing fracture of the right tenth rib. There was also partial collapse of the tenth dorsal vertebral body. These lesions were not present on radiographs taken three months earlier. A skeletal survey at this time showed bilateral femoral lesions from one of which a needle biopsy revealed the presence of highly anaplastic malignant cells. A gallium scan showed increased activity in the femoral lesions and also in the left hypochondrium. Gastric carcinoma with skeletal metastases was the likely diagnosis. When the patient died three months after discharge, post-mortem not only confirmed the presence of a gastric carcinoma but also revealed a large left atrial metastasis (Fig. 3) which extended into the left ventricle and involved the posterior papillary muscle.

DISCUSSION

Cardiac tumours are great imitators in cardiovascular disease and may be extremely difficult to diagnose (Goodwin, 1968). Although all cardiac tumours are rare, secondary tumours are much

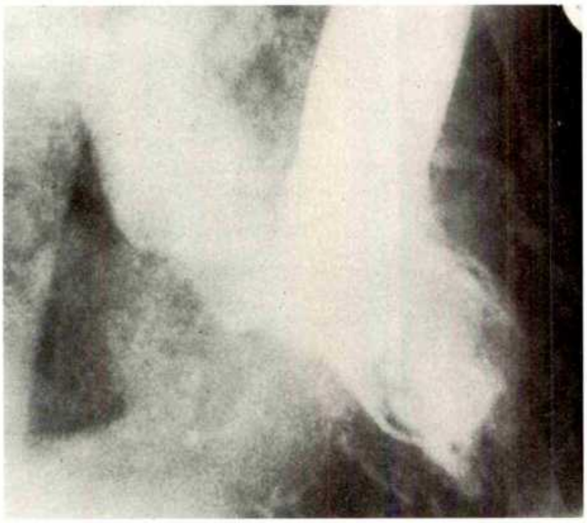

FIG. 1.

Left ventriculogram showing gross mitral reflux.

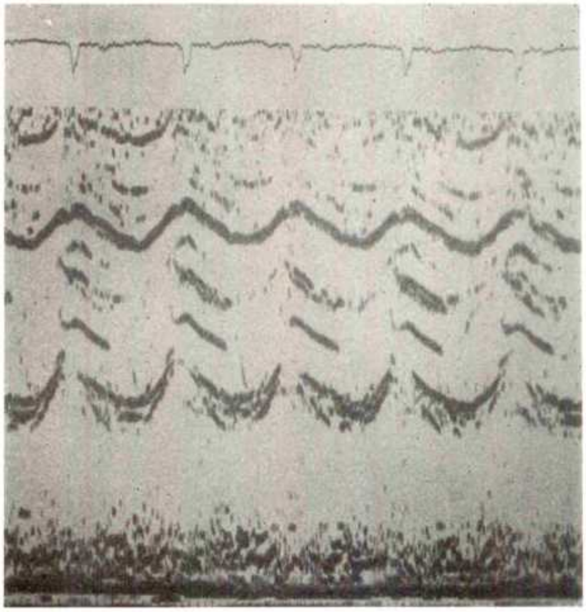

FIG. 2.

Part of ultrasound examination showing an echo-free left atrium lying behind aortic root.

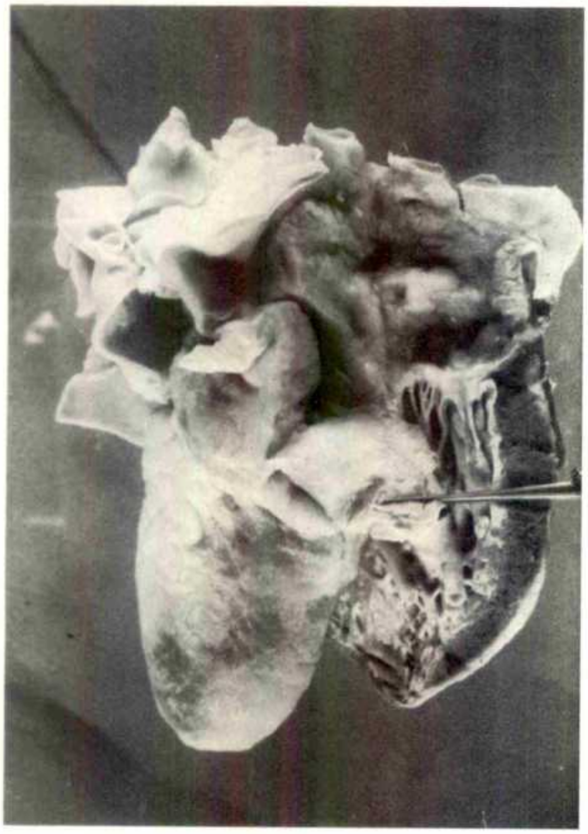

FIG. 3.
Autopsy specimen showing a large left atrial metastasis.

more common than primary tumours (Lymburner, 1934; Lange and Christiansen, 1947). Whilst any malignant tumour may metastasise to the heart or pericardium, bronchial and breast carcinoma, lymphoma (including leukaemia) and malignant melanoma are the most common (Bisel *et al.*, 1953; Young and Goldman, 1954). Endocardial involvement is most frequently encountered in the tricuspid valve (Coller *et al.*, 1950).

It is of particular interest in this case that ultrasound examination did not reveal the presence of a left atrial tumour. Ultrasound is the investigation of choice for suspected myxoma. Atrial myxoma, however, is frequently pedunculated and this allows prolapse to occur into the left ventricle giving rise to the classical pattern of echoes behind the anterior leaflet of the mitral valve.

Left ventriculography showed gross mitral reflux, presumably due to papillary muscle dysfunction because of involvement by tumour but did not detect the left atrial metastasis. Dense contrast medium may have obscured the mass which was presumably smaller at the time of ultrasound and angiographic examination than at post-mortem. Both false positive and false negative results have been previously reported in the angiographic diagnosis of atrial myxoma (Aldridge and Greenwood, 1960; Goodwin, 1963; Ellis *et al.*, 1958). The gallium scan showed increased activity in the gastric and femoral lesions but not in the heart. One can but speculate that uptake in the atrial tumour was similar to that in the surrounding structures, preventing detection. The histology of the gastric and atrial lesions was identical.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Head injuries in children—aetiology, symptoms, physical findings and X-ray wastage

THE EDITOR—SIR

We read the recent paper by Boulis *et al.*, (1978), with great interest and must congratulate the authors on the lucid argument they have advanced to reduce the number of skull radiographs in head injuries in children.

It is interesting that their figures correlate so well with our own findings (Eyes and Evans, 1978). We too found a very low percentage of skull fractures (less than 2%).

In previous series from America (Bell and Loop, 1971; Roberts and Shopfner, 1973) there has been a higher reported incidence of fractures in both child and adult populations. It would seem that in the intervening five or so years, there has been an increasing demand for post-traumatic plain skull radiographs with a diminishing rate of return in terms of positive information. Evans (1977) has already pointed out that the information yield from routine plain skull films in the management of head injuries no longer justified the expenditure involved.

It has long been necessary to give clear cut indications as to the value of, and the time for requesting skull radiographs. We would applaud Boulis *et al.*, for attempting to do this. However, we must disagree with their suggestion that all scalp lacerations require skull radiographs. They have offered no objective proof as to the value of plain skull films in patients presenting with scalp lacerations in isolation. It seems most unlikely that the percentage of fractures detected in patients with scalp lacerations alone would be significant. If a history of penetrating injury is obtained, or other mitigating physical signs are present, then obviously skull radiographs are mandatory.

In no way do we wish to take away any of the impact of this paper, but feel that we must seriously question the suggestion that all scalp lacerations require emergency plain skull radiographs.

Yours, etc.,
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B. EYES.

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(*Received November 1978*)

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(*In reply*).

Head injuries in children—aetiology, symptoms, physical findings and X-ray wastage

THE EDITOR—SIR,

We are grateful for the encouraging remarks of Drs. Evans and Eyes and reply as follows.

1. There will invariably be disagreement by clinicians and radiologists on the indications for skull X rays in trauma. Broadly speaking, clinicians tend to request more examinations, whereas radiologists are conscious of the need to select patients carefully.

2. Our series deals with patients who have had head injuries, namely, blunt trauma to the head. Clearly those children with coma or altered consciousness require skull X rays. There is usually no point in performing an X-ray for a laceration not caused by blunt trauma. Moreover, a blunt head injury associated with a laceration is considered to be more than minor. We feel that scalp lacerations following trauma merit inclusion, since there is a risk of intracranial complications should an underlying fracture be present. Others (Miller and Jennett, 1968; Paediatric Symposium 1965) concur with this.

3. We agree that only a very small number of patients with scalp lacerations had a fracture in our series. However, only 24.9% of those in coma had a fracture. Obviously, the yield of fractures will always be only a fraction of those X rayed, though the indication for X ray be clear. Finally, patients who are vomiting, drowsy or with headache are likely to be admitted to hospital overnight for observation whereas those with laceration as their only sign might well be discharged from Casualty without X ray, and a fracture missed.

Yours, etc.,
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REFERENCES

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Recording media for ultrasound

THE EDITOR—SIR,

I was interested to read the recent article by Meire and Farrant (1978), since I too have been studying the cost advantages and disadvantages of the various recording systems. This study comparing Polaroid, bromide paper and transparent photographic media is now available from the DHSS (1978) having been presented at the Third European Congress on Ultrasonics in Medicine. The conclusions are similar in that the Vidicam system using bromide paper was favoured by our busy ultrasound department both for its convenience and economy. However, all the participants in our study preferred to retain the Polaroid system to enable representative images to be sent back immediately with the patient. Instant prints were also essential for the practical training of radiologists in the use of ultrasound and for discussion and second opinions. The compactness of the Polaroid system renders it invaluable for recording from portable real-time devices. It is worth noting that type 667 film available from Polaroid for medical use is more suitable than the type 107C used in the report by Meire and Farrant. It has better quality control and is cheaper (about 24 pence per image) than type 107C. To make the comparison between Polaroid and other films more

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accurate, the cost of a processor must be taken into account. This may include the capital cost where one is not already available, as well as running expenses, and these will be major considerations for small or isolated departments. The old Polaroid CR9 camera with spreaders is no longer available. Existing cameras can be upgraded on request* to the more satisfactory roller system. Considering grey-scale capabilities—in an ROC analysis that was part of our study, no difference could be detected between Polaroid 667, Vidicam Ilfospeed and Multi-Imager 10×8 NMB film in their ability to display focal liver abnormalities.

Yours, etc.,
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(*Received January 1979*)

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*Polaroid (UK) Ltd., Ashley Road, St. Albans, Hertfordshire.

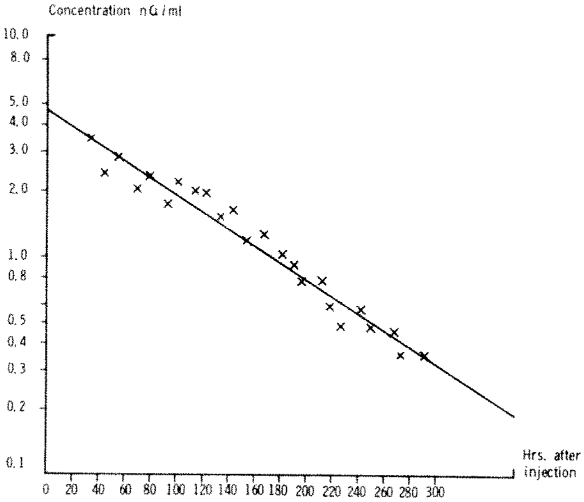

FIG. 1.

Concentration of ^{125}I in breast milk following intravenous injection of 100 μCi ^{125}I labelled fibrinogen.

Excretion of ^{125}I in breast milk following administration of labelled fibrinogen

THE EDITOR—SIR,

The first report (Nurnberger and Lipscomb, 1952) of transmission of radioiodine (^{131}I) to infants through human maternal milk was accompanied by recommendations concerning the diagnostic and therapeutic use of ^{131}I in nursing mothers. Similar information is now available for ^{67}Ga (Tobin and Schneider, 1976), ^{113}In^{m} (Pullar and Hartkamp, 1977), and various ^{99}Tc^{m} labelled radiopharmaceuticals (Vagenakis *et al.*, 1971; Berke *et al.*, 1973; Wyburn, 1973; O'Connell and Sutton, 1976), but none is available for ^{125}I. The use of ^{125}I labelled fibrinogen in the investigation of post-partum deep leg-vein thrombosis in a lactating patient has enabled us to study the excretion of this radionuclide in human breast milk.

After caesarean section a suspected deep leg-vein thrombosis was investigated using 100 μCi of ^{125}I labelled fibrinogen. Following normal practice 400 mg of potassium perchlorate was administered immediately before the injection of labelled fibrinogen, and a three week post-injection course of potassium iodide (150 mg/5 ml once daily) was given. The patient was keen to continue breast feeding but this was discontinued whilst analysis of ^{125}I in sequential milk samples was performed.

Duplicate 2 ml samples of milk were counted in an ICN gammaset together with a simulated ^{125}I standard and the results were corrected to give an activity at the time of expression. The means of the duplicate readings have been used to construct the graph shown in Fig. 1. In no instance was the difference between duplicate readings greater than 3%. It is possible that a sudden change in concentration might have taken place after the twenty-first day when the course of potassium iodide finished, but practical difficulties prevented the collection of milk samples after the twelfth day.

It may be observed that the effective half-life of ^{125}I in the milk is 80 hours which is similar to the half-life of fibrinogen in human plasma (McFarlane, 1964). No attempt has been made, in this series of measurements, to distinguish between protein-bound and free iodine. If the iodine is assumed to be free the effective dose received by the infant's thyroid would be 27.6 rad/μCi. This figure assumes a dose to the adult thyroid of 1200 m rad/μCi and relative sensitivity of adult to newborn thyroid of 1 to 23 (ICRP, 1971).

Assuming milk consumption to be approximately 700 ml/day in the first three months of life and 850 ml/day in the following three months (ICRP, 1975) the effective dose received by the infant's thyroid in the first three months, had breast feeding been continued, would have been 430 rad; 4×10^{-3} m rad would be accumulated in the subsequent six months.

Although there are practical difficulties and there may be local breast complications associated with a resumption of previously suppressed lactation, it does appear from these data that a return to breast feeding after four weeks was at least theoretically possible when the milk radioactivity would have been 1.4×10^{-2} nCi/ml. In this case the subsequent dose to the infant's thyroid would have been of the order of 1 rad.

These results emphasize the desirability of avoiding the use of diagnostic radiopharmaceuticals in nursing mothers. If the use of such materials is unavoidable, discontinuation of breast feeding should be considered.

Yours etc.,
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Radiation doses to extremities—monitoring and limits

THE EDITOR—SIR,

We have recently carried out a series of measurements to provide some detailed information on the radiation doses received during normal duties of two radium custodians working in the Regional Radiotherapy Centre. Monitoring of the extremities had been carried out over a period in the past using rather large and inconvenient detectors strapped to the tip of one finger of each hand, and the doses registered had been assessed in terms of the doses for extremities quoted in the Code of Practice.

In considering these measurements and their assessment we felt that fuller information on the distribution of doses over several points on the hand would be useful. To carry out this more detailed monitoring the two custodians were each provided with a pair of well-fitting nylon gloves onto which five small pockets had been sewn, each of a size suitable to accept one small thermoluminescent disc (8 mm diameter × 0.4 mm thick). The pockets were distributed as follows: (1) on the back of the index finger near its tip; (2) on the back of the 3rd finger near its tip; (3) in the centre of the palm of the hand; (4) on the back of the hand near the knuckles; and (5) on the back of the hand near the wrist.

The monitoring has so far been carried out over five consecutive periods of about two weeks each, though the duration of the periods has not been identical in each case. The discs were of LiF and normal measuring techniques were adopted using a Toledo reader. Table I shows the doses received at the monitored positions recorded in milliroentgens. The doses for each position have been totalled and reduced to a percentage of the doses at the index finger tip for each hand as it was normally the practice to monitor that position when only single measurements were made in the past. The doses received during any one period clearly depend on the number of appliances dealt with during that period and on the type of appliance being loaded; both of these can vary quite significantly between one two-week period and another. To enable a check to be made on the consistency of the positional distribution of doses received by the hands, the results for one custodian are presented in Table II in the form of fractions received at the various positions. These are fractions of the total of the doses received at the five positions on the hand during that period, and presentation in this form goes some way towards counteracting potential experimental variations in the index finger doses taken as the 100% reference levels.

TABLE I

DOSES IN mR FOR FORTNIGHTLY PERIODS A–E

Position (see text)	A	B	C	D	E	Total	%
Custodian A							
Left hand							
1	2200	780	1050	1400	1700	7130	100
2	1900	1100	1100	1500	1550	7150	100
3	1100	590	640	640	900	3870	54
4	680	360	410	500	640	2590	36
5	440	240	185	360	300	1525	21
Right hand							
1	1850	820	1100	1220	1600	6590	100
2	2000	890	900	1000	1250	6040	92
3	940	460	510	880	830	3620	55
4	650	330	430	420	600	2430	37
5	620	300	400	270	570	2160	33
Custodian B							
Left hand							
1	not monitored	1300	790	1250	1220	4560	100
2		1350	790	1100	1100	4340	95
3		880	500	1000	540	2920	64
4		720	320	600	530	2170	48
5		560	230	420	380	1590	35
Right hand							
1		1650	820	1050	800	4320	100
2		1700	880	1050	900	4530	105
3		730	410	720	370	2230	52
4		900	510	600	330	2340	54
5		640	410	470	210	1730	40

TABLE II

INDIVIDUAL POSITIONS AS FRACTIONS OF SUMMATED DOSE DURING EACH PERIOD A–E

Position (see text)	A	B	C	D	E
Custodian A					
Left hand					
1	0.35	0.25	0.31	0.32	0.33
2	0.30	0.36	0.32	0.34	0.30
3	0.17	0.19	0.19	0.14	0.18
4	0.11	0.12	0.12	0.11	0.13
5	0.070	0.078	0.055	0.082	0.059
Right hand					
1	0.31	0.29	0.33	0.32	0.33
2	0.33	0.32	0.27	0.26	0.26
3	0.16	0.16	0.15	0.23	0.17
4	0.11	0.12	0.13	0.11	0.12
5	0.10	0.11	0.12	0.07	0.12

The tables show that, as would be expected, there is a large variation of dose between different positions on the hands during manipulation of radium sources, but they also show that the pattern of distribution between these positions is relatively constant for one individual but not exactly the same for both individuals.

The point of major interest is the interpretation of these monitored doses in the context of published recommendations of maximum permissible doses to the extremities. What are normally referred to as "extremities" are listed in Appendix B of the British Code of Practice (1972) as "hands, forearms, feet and ankles". On the basis of the above measurements it could be held that some kind of average dose over the whole hand is the quantity which should be compared with the maximum permissible dose limit quoted for the hand. Taking into account the wide range of doses demonstrated, we would advance the view that this would be very roughly about one half of the dose to the tip of the index finger.

The recommendations of the ICRP (1978) refer in paragraph 182 to monitoring skin doses. In the case of external radiation the assumption is that "a dose equivalent is measured by one or two dosemeters and the results are treated as representative of the whole, or of substantial areas of the skin. No problem of averaging then arises and the results are related directly to the relevant dose-equivalent limit". Though it is not explicitly stated, the inference appears to be that the radiation field is large enough to deliver a fairly uniform dose to the skin over the whole body. Where contamination is concerned the doses are taken to be non-uniform and the paragraph suggests averaging over an area of about 100 cm². Paragraph 183 refers to accident conditions and suggests detailed information should be sought on the distribution of dose. Averaging should be over 1 cm² and this average dose-equivalent should be compared with dose-equivalent limits quoted for skin.

It is doubtful whether the reasoning of either of these paragraphs can be transferred directly and completely to a discussion of the limits of dose to the hands rather than the skin.

It would, therefore, seem to be important that agreement, or at least a common understanding of the terminology, should be reached so that a quantity referred to as "hand dose" is known to be an average of the dose received at several positions on the hand or, alternatively, that it is taken as the highest dose received at any single point on the hand. In different terms the question would be whether the dose-equivalent limit at present quoted for an extremity specified as "the hand" would have the same value if quoted for a smaller extremity such as "the finger tip".

Yours, etc.,
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Reported *n* and D_q values can be misleading

THE EDITOR—SIR,

Some of the uncertainties in applying survival curves from tissue-culture studies to the prediction of survival probabilities for the treatment of malignant melanoma have been reported previously (Zeitz and McDonald, 1978). An additional uncertainty, which would apply in general in the application of *in vitro* single-cell survival curves in making probability estimates for tumour cell survival with fractionated doses, can be understood from the consideration of two survival curves for Harding-Passey mouse melanoma. Figure 1 shows data originally obtained by Dewey (1971) and later by Dewey and Field (1975) with cells repeatedly subcultured from the same cell line. The methods of growing, treating and scoring colonies were reported to be the same (Dewey and Field, 1975). An analysis of these data, in the manner previously described (Zeitz and McDonald, 1978) gives the results shown in Table I. Here, χ is the reduced chi-square value and P is the probability of exceeding χ^2 for the given reduced chi-square value with the number of degrees of freedom ν. The values obtained by a least square fit with the multitarget expression agree well with those reported by Dewey and Field (1975), $n=11$ and $D_0=92$ rad, which are apparently based on an "eyeball' fit. Thus, the radiation response of the same cell line changed with subculturing; so much so that a multitarget expression fits the later data much better than did the linear-quadratic or the multitarget with non-zero initial slope expression, while the inverse was found for the earlier data. As was pointed out by Dewey and Field (1975), the considerable change in the response of the cells in terms of the shape of the survival curve could have been due to a selective process during prolonged subculturing or other known factors. Regardless of the reasons for the change in shape, these two survival curves can be used to point out the pitfall involved in inferring an increased survival with low-dose fractionation schedules for cells for which a larger *n* or D_q, and about equal D_0's are reported.

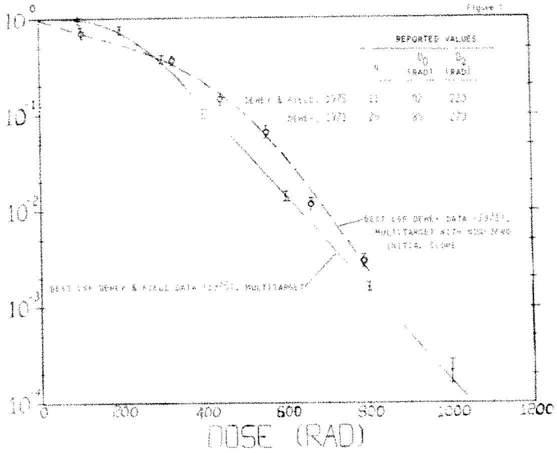

FIG. 1.

The radiation survival data of Dewey (1971) and Dewey and Field (1975), with the best least-square fits (LSF) to the data based on the three models; multitarget, multitarget with non-zero initial slope and linear-quadratic (assumed errors are ±10% in survival and ±2% in dose).

Dewey reported a larger value for *n* (25) for the earlier curve than $n=11$ for the later curve (equivalent to D_q values of 270 and 220 rad) with approximately equal values for D_0. However, the survival probability calculated from the best LSF curves for each set of data, with 31 doses of 200 rad each and using the fractionation model employed by Suit *et al.* (1967), would be 5.7×10^{-9} for the earlier curve and 5×10^{-3} for the later. Thus, reports in the literature of larger values for *n* or D_q, with approximately equal D_0, do not necessarily imply a greater low-dose survival level for the larger *n* or D_q value.

The predicted lower survival probability with multiple low-dose fractionations with the curve for which a larger *n* or D_q value was reported comes about because the parameters used, *e.g.* D_0 and *n*, do not necessarily define the shape of the curve for the best fit. In the particular case under discussion, Dewey (1971) reported parameters D_0 and *n* to define a curve to fit the data. The parameters were inappropriate since they imply a multitarget model yet the data were much better fitted by a continuously bending

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TABLE I

SURVIVAL PROBABILITY ESTIMATES—NOT ALWAYS RELATED TO REPORTED n OR D_q VALUES

Survival data for Harding-Passey cells Source of data	n and D_0 values reported by authors, derived D_q, calculated χ^2 and P; multitarget expression	Least square fit (LSF) multitarget expression D_q, χ^2 and P	Best LSF; either multitarget, linear-quadratic or multitarget non-zero initial slope	Survival probability estimate based on best LSF for 31 × 200 rad Survival probability in bracket is for multitarget expression with the reported n and D_0 values
Dewey (1971)	$n=25$ $D_0=85$ rad $D_q=270$ rad $\chi^2=6.9$ ($P<0.001$)	$n=15\pm4$ $D_0=94\pm4$ rad $D_q=255\pm26$ rad $\chi^2=4.8$ ($P\simeq0.001$)	Multitarget non-zero initial slope $n=53\pm33$ $D_0=108\pm9$ rad $D_1=327\pm54$ rad $\chi^2=0.9$ ($P=0.46$)	5.7×10^{-9} [7.0×10^{-2}]
Dewey and Field (1975)	$n=11$ $D_0=92$ rad $D_q=220$ rad $\chi^2=1.0$ ($P=0.40$)	$n=11\pm2$ $D_0=91\pm3$ rad $D_q=218\pm24$ rad $\chi^2=1.0$ ($P=0.40$)	Multitarget $n=11\pm2$ $D_0=91\pm3$ rad $D_q=218\pm24$ rad $\chi^2=1.0$ ($P=0.40$)	4.9×10^{-5} [7.2×10^{-5}]

curve such as the linear-quadratic expression or the multi-target with non-zero initial slope. These require different parameters to define their shapes.

This analysis adds further evidence to that already given (Zeitz and McDonald, 1978) to show that the significance of the parameters reported in the literature which describe the shapes of survival curves cannot be taken for granted and that, in fact, they may give a qualitatively incorrect impression. If reported survival data are to be used for estimating survival probabilities, it is essential to reanalyze the fit to the data to determine if the reported parameters are appropriate.

Yours, etc.,
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(*Received November 1978*).

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Use of acronyms in describing urinary tract investigations

THE EDITOR—SIR,

I wonder if many of your readers are becoming as confused as I am about the use of acronyms in describing urinary tract investigations. When we use the terms VUR (vesico-ureteric reflux) and IRR (intrarenal reflux), I think most people understand. But how does one describe the investigation in which these occur? After an intravenous investigation one can use the term IVP (intravenous pyelogram), IVU (intravenous urogram) or EU (excretory urogram). After filling the bladder, MCU (micturating cystourethrogram), VCU (voiding cystourethrogram) and even VCG are used. After some experimentation to be trendy and keep in fashion, I have gone back to the old fashioned terms IVP and MCU. The clinicians and everyone else know what I am talking about and certainly in lectures or moments of stress, I naturally revert back to them. Perhaps it does not really matter, but could the editors give some recommendation about the preferred, recommended or likely to become established terms.

Yours etc.,
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Editor's note:

The Editor also uses IVP and MCU, but would not wish to force his foibles onto authors. Readers who feel strongly on the subject might like to state their views.

1979, *British Journal of Radiology*, 52, 676–679

Proceedings of The British Institute of Radiology

Nuclear medicine in paediatrics

Abstracts of papers presented at a joint meeting of the British Institute of Radiology and the Royal College of Physicians of Edinburgh, held on October 20, 1978 at the Scottish Health Services Centre, Crewe Road, Edinburgh

Cardiac and respiratory disease

Chairman: Professor J. O. Forfar

Paediatric cardiology, by D. L. Gilday.

Value of krypton 81m ventilation and ^{99}Tc^{m} macro-aggregate lung scans in children, by I. Gordon, G. Ciofetta and F. Fazio.

The use of Xenon 133 for lung perfusion visualization in children with heart disease, by J. W. Haggith, H. H. Bain, J. D. Fenwick, A. S. Hunter and M. Heppell.

Lung scanning in paediatric practice, by T. H. Macdonald, K. C. Young and P. Horton.

The use of ^{81}Kr^{m} to measure perfusion and ventilation distribution in children—quantitative aspects, by G. Ciofetta, J. M. B. Hughes and M. Silverman.

PAEDIATRIC CARDIOLOGY

By D. L. Gilday

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The analysis of nuclear angiocardiography is divided into two parts. The first is visual inspection and assessment of the analogue images produced by the gamma camera. These images provide a useful pictorial demonstration of the flow of the bolus through the heart and lungs. The detection of a large left to right shunt is usually seen by this method. Other congenital anatomical defects can also be seen.

The main method of analysis of the data regarding left to right shunting is via computer assessment of the time-activity histogram of the transit through the lungs. The gamma variate analysis of the histogram has an excellent correlation with the Dye and Fick dilution methods (Treves and Malta 1974). The evaluation of right to left shunts can be carried out very effectively using the method described by Gates *et al.* (1971) which involved the injection of radioactively labelled microspheres of albumin which would impinge on the first vascular bed encountered. This resulted in a biological distribution of the tracer according to the output of the right ventricle. Thus, by quantifying the amount of activity within the lungs as compared with the whole body, one can get an estimate of the amount of blood going to the lungs and the amount of blood shunted.

Of recent marked interest is the use of thallium 201 chloride in the evaluation of paediatric heart disease in the newborn. The differentiation of global ischaemia (transient myocardial ischaemia) is very important in that the patient may present as if there was congenital heart disease. The appearance in the thallium scan of minimal activity within the myocardium suggests this diagnosis. In addition the anomalous left coronary artery will cause a defect in the perfusion to the myocardium which is readily assessed. Infundibular hypertrophic subaortic stenosis and other cardiomyopathies are readily detected, diagnosed and differentiated one from another. With the addition of the multiple gated acquisition study one can also assess the overall function of the left ventricle at that time.

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VALUE OF KRYPTON 81m VENTILATION AND ^{99}Tc^{m} MACRO-AGGREGATE LUNG SCANS IN CHILDREN

By I. Gordon, G. Ciofetta and F. Fazio

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Krypton 81m has a ½ life of 13 sec and is a pure γ emitter at 190 KeV. It is eluted from a rubidium generator, the ½ life of which is 4.5 hours. The latter is produced by a cyclotron. The child lies supine on the gamma camera and the rubidium generator is eluted with humidified air. An intravenous injection of ^{99}T^{m} macro-aggregate are injected at the start of the examination.

The patients examined fall into four main groups:

(*A*). *Establish the diagnosis.*

This is a relatively small group of patients in whom the combined ventilation/perfusion has either suggested the exact diagnosis or directed the attention of the clinician and diagnostic imager to the abnormal area where the diagnosis has been tentatively suggested.

(*B*). *The evaluation of surgical procedures on the pulmonary artery.*

This technique is valuable in assessing the post-operative patency of the relevant pulmonary artery and thereby the vascularization of the relevant lung.

(*C*). *Refute a diagnosis.*

A normal ventilation/perfusion scan in a child suspected of having either bronchiectasis or a foreign body is very strong evidence that there is no significant disease present. Both anterior and posterior oblique projections must be obtained as well as PA and lateral radiographs. Fluoroscopy is also essential in cases of suspected foreign body.

(*D*) *To establish the extent of the disease.*

Ventilation/perfusion scans are proving to be a very sensitive index of the extent of lung disease in children with chronic lung disease. In children with bronchiectasis who are not responding to adequate active medical therapy and in whom surgery is therefore contemplated, a high quality ventilation/perfusion scan with all four oblique projections may alleviate the need for bronchography.

It is essential to combine the information from all modalities of diagnostic imaging step by step in order that the next relevant examination will be carried out. In an area where so many different modalities of investigation are available it is essential that problem-oriented paediatric imaging is practised.

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THE USE OF XENON 133 FOR LUNG PERFUSION VISUALIZATION IN CHILDREN WITH HEART DISEASE

By J. W. Haggith, H. H. Bain, J. D. Fenwick, A. S. Hunter and M. Heppell

Regional Medical Physics Department, Newcastle upon Tyne

This preliminary study was to determine the relative pulmonary perfusion in 16 children with congenital heart disease. The technique involves an intravenous bolus injection of ^{133}Xe in saline with the patient positioned supine over a gamma camera. No special preparation of the patient is required. Serial two-second posterior views of the lungs are obtained using a data-processing system. Time-activity curves are created for each lung from which the relative lung perfusion may be determined. Right to left shunting can also be detected.

These curves facilitated an estimate of the radiation dose. In these patients, for an administered activity of 0.2 μCi/kg body weight, the dose is not greater than 10 mrem whole body and 15 mrem to the lung mucosa.

The technique has been used to demonstrate relative perfusion in patients with systemic arterial to pulmonary arterial anastomoses, with pulmonary stenosis and with pulmonary vascular disease. The method is safe and relatively non-invasive and may prove valuable in the long-term management of these patients.

LUNG SCANNING IN PAEDIATRIC PRACTICE

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Department of Clinical Physics and Bio-Engineering, Glasgow

Regional lung function studies are of value in paediatrics particularly between 18 months and 5 years, a period when standard lung function tests are rarely applicable. Since September 1976 we have performed almost one hundred lung scans in children aged six weeks to seven years. These studies were performed using ^{133}Xe. Ventilation and perfusion studies were performed in the upright position using a gamma camera linked to a data analysis facility. Lung images were recorded at one second intervals, were displayed on a colour television screen, and analysed to determine distribution indices and mean fractional turnover rates for the upper and lower zones of each lung. The distribution indices were helpful in identifying small lungs or lung areas with a reduced contribution to ventilation or perfusion, *e.g.* bronchiectasis. In the latter case non-functioning lung tissue could be removed. Reduction in distribution and of fractional turnover was used to identify conditions such as the hypoplastic lung syndrome, and a pattern of ventilation and perfusion mismatching, together with reduced turnover rates, to identify a diffuse emphysema in a very young infant. In one patient, turnover in the perfusion study was considerably prolonged when compared with the ventilation study. Biopsy demonstrated pulmonary eosinophilia. The abnormality in the perfusion study reverted to normal with corticosteroid therapy and treatment could be monitored by the use of lung scans. Children who had radiotherapy for lung secondaries from solid tumours, *e.g.* Wilm's tumour, showed some reduction in distribution to the lung receiving radiotherapy. This reverted to normal after many months.

In 33 children with scoliosis we have shown that the bias (the percentage by which the activity of the more active lung exceeds the less active) of perfusion and ventilation increases as the angle of curvature increases. Preliminary findings also suggest that perfusion is reduced in the concavity of the curve but this matter requires further investigation.

In conclusion we would suggest that with the scintillation camera facilities available in most teaching hospitals, a clinician (in this case a paediatrician) can obtain information which is of relevance in the routine clinical care of patients.

THE USE OF ^{81}Kr$^{\text{m}}$ TO MEASURE PERFUSION AND VENTILATION DISTRIBUTION IN CHILDREN – QUANTITATIVE ASPECTS

By G. Ciofetta*, J. M. B. Hughes and M. Silverman

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The continuous inhalation of ^{81}Kr$^{\text{m}}$ ($t_{\frac{1}{2}}$ 13 sec) allows images of lung ventilation to be recorded using a gamma camera (Fazio and Jones, 1975). Detection of regional ventilation defects is possible using this technique during normal breathing and therefore without the patient's co-operation and with minimal radiation exposure.

Application of ^{81}Kr$^{\text{m}}$ ventilation studies in children is complicated by the very fast ventilatory turnover (V/VOL) frequently found in neonates and infants. Under these conditions equilibrium between regional inspired and expired isotope concentration may occur, despite the very rapid physical decay and the ^{81}Kr$^{\text{m}}$ images may reflect lung volume rather than ventilation distribution.

Images recorded during continuous intravenous infusion of ^{81}Kr$^{\text{m}}$ dissolved in 5% dextrose, reflect lung perfusion but are also affected by the distribution of ventilation. This occurs because radioactive gas evolved into the alveoli is removed by ventilatory washout (V/VOL) (Ciofetta *et al.*, 1978). It is possible to measure ventilatory washout (V/VOL) regionally in absolute units (1. min^{-1}. 1^{-1}) from the clearance curves of inhaled and infused ^{81}Kr$^{\text{m}}$.

This measurement allows a more accurate interpretation of the ^{81}Kr$^{\text{m}}$ ventilation and perfusion images in infants and children. Some practical examples were presented to illustrate the clinical use of this quantitative analysis.

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Urinary tract

Chairman: Professor J. S. Robson
Measurement of separate renal function with $^{197}HgCl_2$, by C. Raynaud.
Early detection of renal damage, by M. V. Merrick, W. S. Uttley and R. Wild.
Direct radionuclide cystography, by A. R. Constable.
A comparison of nuclear medicine and excretion urography in the follow-up of ileal loop diversion, by J. D. Orr, M. V. Merrick, R. Wild and I. S. Kirkland.

MEASUREMENT OF SEPARATE RENAL FUNCTION WITH $^{197}HgCl_2$

By C. Raynaud

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When radiomercury is injected in soluble form such as $^{197}HgCl_2$, renal activity rises slowly to a plateau of 19 to 19·5% of the injected dose in the normal subject, within 24 hours. It remains at this level for several days. Uptake, generally measured at the second or the third day, depends on the functional activity of the renal parenchyma. It is increased if renal function is increased, and decreased if renal function is decreased. It is significantly correlated with inulin and PAH clearances, and Tm of PAH.

The measurement is generally made by quantitative scintigraphy using a gamma camera or a rectilinear scanner. Two corrections are used, one for kidney depth, the other for liver interference. Results calculated as a percentage of the injected dose are finally expressed as a percentage of normal, the normal values being 100±13% of normal mean for each kidney, and 100±11% of normal mean for global uptake.

The Hg uptake test is useful to the urologist who needs a reliable measure of the functional state of each kidney, for example in obstructive uropathies, where he must decide between conservative surgery and nephrectomy. It is also useful when evaluating the efficiency of medical or surgical therapy. It is especially useful when assessing compensatory hypertrophy.

The weakness of this technique is the radiation dose absorbed by the kidneys, which amounts to 9 rad in young children. Attempts to replace $^{197}HgCl_2$ by $^{99}Tc^m$-DMSA, $^{99}Tc^m$-TMA, and radioactive bismuth were not successful, due to the lack of reproducibility with DMSA and TMA, and high urinary excretion of Bi.

If carefully controlled, by arteriography for example, the Hg uptake test temains extremely useful.

EARLY DETECTION OF RENAL DAMAGE

By M. V. Merrick, W. Uttley and R. Wild

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Radioisotope imaging of the kidney (RIK) was compared with excretion urography (EU) in 79 children (155 kidneys) with urinary tract infections. Scans were performed not less than one hour after the intravenous administration of 75 μCi/kg of technetium dimercaptosuccinate. The standard radiographic technique of EU was modified as necessary by the radiologist performing the examination.

Ninety-seven kidneys were considered normal by both techniques; in a further 46 both were abnormal, and showed a similar extent of renal cortical loss. There was a discrepancy in 12 cases. Cortical loss was present on the EU in three children with a normal RIK. In one case there was movement on the RIK. The other two had concentric cortical loss. Defects were present, and were more extensive on the RIK than on EU, in nine kidneys. These were segmented defects not associated with deformation of the perirenal fat.

It is concluded that the RIK is more sensitive than EU for detecting segmented scars, but the EU is the better technique for the detection of concentric cortical loss.

A technique of detecting vesico-ureteric reflux (VUR) at the end of the renal function examination using TcDTPA was described. The technique is comparable in sensitivity to the radiographic micturating cystourethrogram, but avoids the need for catheterization.

DIRECT RADIONUCLIDE CYSTOGRAPHY

By A. R. Constable

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During the normal course of diagnosis and treatment of vesico-ureteric reflux (VUR), children will frequently be exposed to a considerable radiation dose from intravenous urograms (IVU's) and micturating cystourethrograms (MCU's).

Radionuclide cystography (RNC) normally results in a radiation dose about a hundred times smaller than the corresponding radiographic procedure. The diagnostic reliability of RNC has been shown to be similar to that of MCU and this, together with the favourable dosimetry, suggests that the technique should be included in the normal management protocol for these patients. Although the quest for a completely atraumatic VUR investigation favours the indirect RNC methods, the direct (per catheter) method is generally thought more suitable for children and for patients with outflow abnormalities.

The results of a recent study comparing radiographic and radionuclide techniques and the place of RNC in a suggested protocol were discussed.

A COMPARISON OF NUCLEAR MEDICINE AND EXCRETION UROGRAPHY IN THE FOLLOW-UP OF ILEAL LOOP DIVERSION

By J. D. Orr, M. V. Merrick, R. Wild and I. S. Kirkland

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Progressive deterioration of the upper urinary tract occurs in many children who have undergone urinary diversion. Early detection of this deterioration is difficult as biochemical investigations give little indication of early damage, and although excretion urography gives adequate morphological detail of the kidney, it is not a satisfactory method of assessing renal function. It is hoped that more sophisticated radioisotope techniques might detect change at an early stage.

A small group of 24 patients in whom the original indication for diversion had been myelomeningocoele were investigated, on average 12 years after operation. From this group 47 kidneys were available for study. The excretion urogram was carried out in a standard manner. The radioisotope investigations were performed using a gamma camera on line to a dedicated mini-computer. For the initial dynamic study "renograms" were obtained utilizing ^{99}Tc^{m} DTPA, and on the following day renal scans were obtained 2–4 hours after injection of Tc DMS. The results obtained from the differing techniques were then compared. On initial comparison both techniques were found to be in concordance in 85% of the kidneys compared, but when the amount of information obtained from each investigation was considered, although found to be similar in 75%, in 17% the radioisotope methods gave more information. Overall the combined radioisotope technique gave more information concerning the morphology, total renal function and relative function of both kidneys, especially when renal function was poor. Scanning could be carried out at lower risk, lower radiation dose and lower cost. Therefore, it is considered a suitable method of follow-up in this group of patients. Where necessary further morphological information can always be obtained from the excretion urogram.

General topics

Chairman: Dr. J. P. Lavender

Bone imaging in paediatrics, by D. Gilday.

Gastro-intestinal haemorrhage unrelated to gastric mucosa diagnosed on ^{99}Tc^{m} pertechnetate scans, by I. Gordon.

BONE IMAGING IN PAEDIATRICS

By D. Gilday

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Since the introduction of the phosphate compounds for bone imaging there has been a dramatic utilization of bone scans in paediatric diseases. In most benign diseases of bone the addition of immediate post-injection blood pool images has proven to be extremely valuable in assessing the degree of hyperaemia of the lesion. The use of high resolution and magnification pinhole views in the imaging of lesions, especially those which are avascular, is very important. The focal accumulation of bone radiopharmaceutical associated with the intra-osseus hyperaemia has proven to be a very reliable indicator of osteomyelitis and to separate the latter from cellulitis. The viability of bone after trauma can be readily assessed especially with magnification views. Skeletal pain in childhood is often a diagnostic dilemma, the cause of which can be both detected and characterized by bone imaging. This is especially so in the diagnosis of occult, axial skeleton osteoid osteomas. Although the detection of Legg-Perthes disease is usually made radiologically, in some instances the radiographs may be normal where the bone scan will demonstrate absent deposition of radiotracer in the femoral head, indicating the avascular nature of the disease. Re-vascularization of the femoral head can be readily assessed by the bone scan as it is a sensitive indicator of bone and blood flow.

Neoplasia, both primary and secondary, involving the skeleton can be better assessed by bone scanning using screening gamma camera images and selective high quality, high resolution or magnification images, rather than by radiological skeletal survey (especially in neuroblastoma, lymphoma, leukaemia and bone secondaries from osteogenic and Ewing's sarcoma).

There are some difficulties in the use of bone imaging in childhood such as the contamination of the skin with radioactive urine which must be prevented at all costs, and the involuntary voiding on the part of young children and infants which may lead to contamination of the clothes or pyjamas.

GASTRO-INTESTINAL HAEMORRHAGE UNRELATED TO GASTRIC MUCOSA DIAGNOSED ON ^{99}TC^{m} PERTECHNETATE SCANS

By I. Gordon

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Small bowel bleeding due to an anastomotic ulcer in one patient and a haemangioma in another were diagnosed by ^{99}Tc^{m} pertechnetate radioisotope scans. Multiple views of the abdomen during the radioisotope scan proved essential. The rationale of this technique for imaging in cases of haemorrhage from the gastro-intestinal tract was described.

1979, *British Journal of Radiology*, *52*, 680–661

Proceedings of The British Institute of Radiology

NMR imaging*

Abstracts of papers presented at a joint meeting of The British Institute of Radiology, The Institution of Electrical Engineers and the Institution of Electrical and Radio Engineers on November 16, 1978 in the Faraday Room at The Institution of Electrical Engineers, Savoy Place, London WC2R OBL

Imaging by nuclear magnetic resonance and its biomedical implications, by J. Mallard, J. M. S. Hutchison, W. Edelstein, M. Foster and R. Ling.
NMR imaging at intermediate sizes, by E. R. Andrew, P. A. Bottomley, W. S. Hinshaw, G. N. Holland, W. S. Moore, C. Simaroj and B. S. Worthington.
Human whole body imaging by NMR, by P. Mansfield.
Physical limits to NMR imaging, by W. S. Hinshaw (*no abstract received*).

IMAGING BY NUCLEAR MAGNETIC RESONANCE AND ITS BIO-MEDICAL IMPLICATIONS

By John Mallard, J. M. S. Hutchison, W. Edelstein, M. Foster and R. Ling

Department of Bio-Medical Physics and Bio-Engineering, University of Aberdeen

Nuclear magnetic resonance imaging of proton concentration within a tissue sample can be achieved by superimposing a magnetic field gradient upon the static magnetic field of an NMR spectrometer. In addition, by using pulsed techniques, the spin-lattice relaxation time, T_1, can be imaged.

A system operating at 1·7 MHz is being built in Aberdeen using an air-cored magnet and a selective excitation technique to provide position data from adjacent lines, from which the image of transverse sections across any part of the human body can be built-up: relaxation time is displayed independently from proton concentration. Spatial resolution depends upon differences in T_1 from tissue to tissue and is expected to be better than 1 cm for trunk imaging.

The T_1 over 50 different tissue types from animal and human post mortem samples have been measured at 24 MHz, and range from 150 to 800 m sec. The values are believed to be related to the closeness of the binding of water to macromolecules in the tissues. This five-fold range may lead to a significant improvement in the imaging of soft tissues and any pathological state which affects the water balance or binding of water within them, oedema being an example. While the imaging of tumours should prove possible, it is questionable whether this will be the major clinical use of the technique and its real contribution may be for conditions which, at present, are not amenable to other existing imaging procedures.

NMR IMAGING AT INTERMEDIATE SIZES

By E. R. Andrew, P. A. Bottomley, W. S. Hinshaw G. N. Holland, W. S. Moore, C. Simaroj

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Good quality proton NMR images of potential medical and biological usefulness have been produced by the multiple sensitive point method of NMR imaging (zeugmatography) (Andrew *et al.*, 1977, Hinshaw, 1974, 1976). An instrument has been developed which operates at 30 MHz for protons and has a specimen access of 8 cm diameter. A thin transverse section of the specimen, a few mm thick, is defined and scanned in 5 to 15 minutes. The images consist of 128 × 128 picture elements and have a resolution of 0·5 mm. Images have been obtained of thin sections of a live human hand, wrist and forearm, and of small animals (rabbit and rat). Good tissue discrimination is displayed with excellent correspondence to the actual anatomical features in sections subsequently cut (in the case of human images similar cadaver sections were cut for comparison) (Hinshaw *et al.*, 1977; 1978; 1979).

No radio frequency attenuation was evident in the images, and calculations suggest that for whole-body imaging this should not be too serious at frequencies below 10 MHz (Bottomley and Andrew, 1978). Current extension of proton NMR imaging to whole-body sizes is therefore practical in fields up to about 0·2 T. ^{19}F NMR images have also been obtained using phantoms and may have applications in conjunction with fluorinated pharmaceuticals and blood substitutes (Holland *et al.*, 1977); extension to ^{31}P and other nuclei may also be of interest. Advantages of this method of medical imaging are its lack of hazard, the penetration of bony structures and its possible discrimination of pathological tissues through relaxation differences. Further details of the work are given in the references below.

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HUMAN WHOLE BODY IMAGING BY NMR

By P. Mansfield

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Progressing from our small scale nuclear magnetic resonance (NMR) line-scan imaging studies (Mansfield and Maudsley, 1976; 1977), which established the viability of using NMR to visualize anatomical detail in living fingers, we have now expanded the apparatus (principally the magnet) so that human whole body thin slice cross-sectional pictures can now be made. The first live line-scan image was produced with the full-scale apparatus earlier this year (Mansfield, *et al.*, 1978). Current interests are concerned with detailed evaluation of NMR images obtained from cadaver tissue and some preliminary results of this work were presented.

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We have also used the apparatus to study tumorous whole breasts in operation samples following mastectomy. Results were presented which demonstrated for the first time, localization of a carcinoma in a whole breast (Mansfield *et al.*, 1979). Line scan imaging, while being useful in general evaluation of the NMR imaging technique has severe limitations in imaging time for a given picture quality. Our interest is therefore turning more to ultra high-speed planar imaging methods (Mansfield and Pykett, 1978), which in terms of speed and picture quality seem to approach the optimum achievable from the point of view of information theory.

Finally, the idea of using NMR to produce two dimensional shadowgraphs as in normal X-ray techniques, was discussed and a preliminary result for a live human hand presented as a demonstration of its feasibility and possible usefulness.

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New methods of imaging in nuclear medicine

Abstracts of papers presented at a joint meeting with the Royal College of Radiologists, the Royal Society of Medicine, section of Radiology and The British Institute of Radiology held on Thursday, February 15, 1979 at Institute House, 32 Welbeck Street, London W1M 7PG.

Longitudinal tomography, by M. J. Myers
Emission computerized axial tomography, by W. I. Keyes
Multiwire imaging devices, by J. E. Bateman
Positron emission imaging, by T. Jones

LONGITUDINAL TOMOGRAPHY

By M. J. Myers

Department of Medical Physics, Hammersmith Hospital, London W12 0HS

The main features of longitudinal tomography that distinguish it from conventional imaging and from transverse tomography were outlined; for example, since all planes in the body are viewed simultaneously, their images interfere with each other and they can only be partially separated mathematically, as distinct from transverse tomography where each plane is separated exactly by physically limiting the fields of view.

Two imaging devices were described and clinical examples from each presented. The one is a commercial instrument based on two scintillation cameras which are scanned over the body. Up to 12 longitudinal sections are produced by electronically repositioning the images on the crystal detectors to bring each section into focus. The other device is simpler and is based on a large solid-angle focused detector which scans each plane in turn.

A method of separating the planes from each other by digitizing the images, calculating the contributions of other planes and then subtracting them from the plane of interest was also described. The direct production of longitudinal tomograms may, in the future, be superseded by constructing them from a series of contiguous transverse sections, but longitudinal tomography may find a place in fast dynamic sectional imaging using large area detectors and positron emitters.

EMISSION COMPUTERISED AXIAL TOMOGRAPHY

By W. I. Keyes

Department of Bio-Medical Physics and Bio-Engineering, University of Aberdeen

Transverse-section emission tomography has provided an exciting opportunity to quantify with high spatial resolution the distribution of radionuclides *in vivo*. Using camera or scanner systems in conjunction with readily available gamma-emitting radionuclides, particularly ^{99}Tc^{m}, transverse section studies have been shown to enhance the value of conventional static imaging and to offer real quantitative potential. The technique was examined in terms of how and why it works, how different equipment is being used to the same ends, what sort of clinical results are being obtained and what the major problems and limitations are.

The response of different systems to point, line and distributed sources was investigated as an illustration of how a system may be calibrated for measurement of absolute concentration of activity in terms of μCi per cm^3. The relative sensitivity of the different systems, existing and proposed, was tentatively examined in terms of useful exposed crystal area.

Reprints of these abstracts may be obtained free on applicayion to the Managing Editor, BRITISH JOURNAL OF RADIOLOGY, 32 Welbeck Street, London W1M 7PG (01–935 6867)

MULTIWIRE IMAGING DEVICES

By J. E. Bateman

Rutherford Laboratory, Harwell, Oxon

Multiwire proportional counters have been something of a success story in high energy and nuclear physics since their emergence some ten years ago. Detectors capable of imaging charged-particle distributions in one or two dimensions have been developed with (at one end of the scale) apertures of up to 3 × 4 m and spatial resolution of 1 mm, while at the other end of the scale small detectors capable of resolving 0.05 mm have been developed. High counting rates of $> 10^5$ counts $\text{cm}^{-2}\ \text{sec}^{-1}$ can be supported in many multiwire devices.

In the case of X and gamma rays, conversion of the neutral particle into a charged particle (a fast electron) is an essential first step. The operating medium of the multiwire counter being a gas (*i.e.* low density), we find that the conversion process is the area of greatest difficulty in the successful application of multiwire counters to radiology.

Two separate approaches are taken.

(i) In the low energy range (<60 keV) a suitable gas of high atomic number (xenon) is used both as converter and amplifying gas. As an example of this approach a system is described which was developed at the Rutherford Laboratory for a research programme on osteoporosis (using X-ray absorptiometric imaging) at the MRC Mineral Metabolism Unit at Leeds General Infirmary.

(ii) As the gamma-ray energy becomes higher (say for example $^{99}\text{Tc}^{\text{m}}$ at 140 keV), recourse is had to the so-called "hybrid" detector. In this device the conversion process takes place in solid material from which the fast electrons can escape into the gas of the multiwire counter.

At the Rutherford laboratory two applications have been investigated—a multiple multiwire counter using tin-foil cathodes for $^{99}\text{Tc}^{\text{m}}$ imaging and a similar device using lead foil cathodes for imaging with positron annihilation radiation. Results from both the developments are presented.

The state of commissioning of the 30 × 30 cm positron camera being developed for the MRC Cyclotron Unit, Hammersmith, was described, and some images from other multiwire systems presented to show the potential for radiopharmaceutical imaging using the multiwire positron camera.

POSITRON EMISSION IMAGING

By T. Jones

MRC Cyclotron Unit, Hammersmith Hospital, London W12 0HS

Positron-emitting tracers offer certain physiological and physical advantages as *in vivo* tracers. Hence it is appropriate to assess positron emission imaging as a whole and not solely from the instrumental point of view. There are basically two categories of positron emitters used for *in vivo* studies: those produced by a cyclotron, in particular $^{15}\text{O}_2$, $^{13}\text{N}_2$, ^{11}C and ^{18}F, and those produced from generators notably ^{82}Rb and ^{68}Ga. The physiological advantages of these tracers relative to those used commonly in nuclear medicine are self evident. The physical advantage of the positron emitters stems from the concept of utilizing coincidence detection of the annihilation photons. This mode of measurement offers, relative to that of single photon detection, higher accuracy with respect to uniformity of spatial resolution in depth and an ability to correct absolutely for tissue attenuation. This in turn is clearly advantageous in effecting tomographic measurements of a tracer's distribution *in vivo*.

In the forseeable future these tracers should be used to obtain knowledge of the regional physiological consequences of disease and the effects of therapy rather than for attempting to develop routine diagnostic procedures. The projected clinical scientific programme at Hammersmith with a positron ECAT is concerned with the brain, myocardium and lungs.

In order to effect this programme an appropriate positron ECAT device had to be selected. There were two categories of tomographic systems to be considered, area positron cameras and those devices which confine data collection to a single transaxial slice. Accuracy was foremost in our assessment and led to the single slice design being selected for our programme. This decision was reached bearing in mind that area cameras are subject to scatter and random coincidences which in turn have the effect of imposing a high noise component on the recorded data.

Book review

Intensive Care Radiology. Imaging of the critically ill. Eds. L. R. Goodman and C. E. Putman. pp. xiv + 363, illus., 1978 (C. V. Mosby, St. Louis; Henry Kimpton, London), £29·00.
ISBN 0–8016–1894–0.

This is a 350 page book attempting to coordinate the special information required for the management of one particular group of patients. It contains information related to many aspects of medical care and applied physiology with its main emphasis on radiology.

Approximately half the text deals with aspects of chest radiology and the remainder attempts to cover the abdomen and special procedures including arteriography, ultrasound, nuclear medicine, radiographic physics and resuscitation.

Clearly with such a wide base, detailed study cannot be achieved. Most radiologists will find the information very basic but the book may appeal to junior medical staff with little experience in management of patients in this area of medical practice.

Some of the illustrations are rather poor. It is an American text with the apparently unavoidable abbreviations and lists. For ARDS (adult respiratory distress syndrome) 30 associated diseases are listed together with 26 synonyms. The discussion and illustration of the clinical, pathological and radiological features of this "syndrome" are complete in 13 pages.

A. B. Ayers

Forthcoming events

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of the penultimate month preceding publication (*i.e.* April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

IV EUROPEAN CONGRESS OF RADIOLOGY

The IV European Congress of Radiology will take place in Hamburg (German Federal Republic), September 4–8, 1979.

Scientific programme:

diagnostic research of organs of the upper abdomen;

diagnostic research in nuclear medicine: organs of the upper abdomen;

radiotherapy in tumours of the genital system of males and females;

radiobiology and X-ray protection (combined therapies and risks of ray exposure);

radiophysics and techniques (methodical problems in diagnostics and in planning of radiotherapy).

Enquiries: Secretary of the IV European Congress of Radiology, Postfach 10 64 07, D-2000 Hamburg 1, Federal German Republic.

QUANTITATION OF TUMOUR RESPONSE: A CRITICAL APPRAISAL

The L. H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to stimulate a critical appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.

Factors of prognostic significance.

In vitro assays of tumours excised after treatment *in vivo*.

The choice of suitable experimental models in rodents.

The role of human tumour xenografts.

Statistical evaluation of tumour response data.

The limitations and artefacts of each assay technique.

The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

PAEDIATRIC RADIOLOGY

A two-day course in diagnostic paediatric imaging will be held at the Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London WC1 on November 15–16, 1979. The main theme of this course will be the respiratory/cardiovascular system.

Further details and application forms are available from The Secretary, Department of Paediatric Radiology, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

THE BRITISH MEDICAL ULTRASOUND SOCIETY
11TH ANNUAL SCIENTIFIC MEETING

To be held on December 17–18, 1979 in Edinburgh.

Authors wishing to submit contributions for consideration should send the title and 100–200 word abstract to the address below before September 15, 1979. Additional background information on the work would help in planning the programme.

Address for enquiries: Dr. W. N. McDicken, Department of Medical Physics and Medical Engineering, The Royal Infirmary, Edinburgh EH3 9YW.

COMPUTED TOMOGRAPHY IN ONCOLOGY

ESCAT 2, European Seminar on Computed Tomography in Oncology, will be held at the Excelsior Hotel, London, Heathrow from February 4–7, 1980.

The meeting will be of interest to radiologists, physicists, radiotherapists and members of related disciplines and there will be invited speakers from Europe and the USA, together with a limited number of proffered papers.

Topics include primary diagnosis; staging; therapeutic response; radiotherapy treating planning; tissue characterization.

Further information from: Dr. Janet Husband, Organizing Secretary, The Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT.

5TH INTERNATIONAL CONGRESS OF THE INTERNATIONAL RADIATION PROTECTION ASSOCIATION

Will take place in Jerusalem, Israel, March 9–14, 1980.

The scientific programme of the Congress will cover all aspects of radiation protection with emphasis on its central theme: radiation protection—a systematic approach to safety.

An interesting programme has been planned including a commercial exhibition and pre- or post-congress workshops and Professional tours.

Social events and a programme for accompanying persons have been organized.

For further information: The Secretariat, 5th International Congress of IRPA., PO Box 16271, Tel Aviv, Israel.

SYMPOSIUM ON SPINE AND ITS CONTENTS

EAR "Symposium Vertebrologicum" (Spine and its Contents) will be held from April 23–25, 1980 in Prague, Czechoslovakia.

The subjects of this symposium will be recent advances and experiences in:

(a) Equipments and investigative methods of spine and spinal cord.

(b) Radioanatomy and physiology of spine and spinal cord.

(c) Radiodiagnosis of pathological conditions.

(d) Interventive (diapeutic) radiodiagnostic methods.

For further information contact The secretariat of "Vertebro 1980", PO Box 88, Sokolská 31, 120 26 Praha 2, Czechoslovakia.

XV INTERNATIONAL CONGRESS OF RADIOLOGY

The XV International Congress of Radiology will take place June 24–July 1, 1981 in Brussels, Belgium.

The scientific activities of the Congress as well as the scientific and technical exhibitions will take place in the Brussels Exhibition Centre.

Further information from: Secretariat ICR-81, Ave. Winston Churchill 234B-Box 16, B-1180 Brussels, Belgium.

Forthcoming events

TENTH L. H. GRAY CONFERENCE

Will be held in Oxford on July 13–16, 1981 on "Biological Actions of Radiofrequency, Microwave and ultrasonic Radiations".

A conference to review and discuss past and current research on the radiobiology and biophysics of the radiations, particularly in relation to their potential therapeutic value.

Information/Chairman of Organizing Committee: Dr. C. R. Hill, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey.

Book reviews

Computer methods: The Fundamentals of Digital Nuclear Medicine. By David E. Lieberman, pp. xviii+225 (C. V. Mosby Company, St. Louis; Distributed in UK by Henry Kimpton, London). £11·00.
ISBN 0–8016–3009–6.

The preface to this book says that it was written to fill a gap and it is a pleasure to agree with the author that it does fill a real need. This is not a book for computer scientists and electronics specialists; it is a book for doctors, radiographers, medical physicists and anyone working in the field of nuclear medicine generally. One often gains the impression from doctors that they feel there is a great deal of mystique surrounding computers when used in such applications as attachment to gamma cameras. This book explains it all in very simple terms, yet not so simple that it contains no "meat".

The first two chapters would serve as an elementary introduction to almost any field of computing and could be skipped by some readers. Chapter 3 launches straight into the nuclear medicine problem but gives also some very useful background information on data storage media such as discs and tapes. The diagram on page 28 ought to be reproduced more often: it illustrates the size of dust particle that can interfere with the satisfactory operation of a disc.

The book covers a wide range of topics including image enhancement, dynamic function studies, computer tomography and nuclear cardiology. The work is very valuable as a source of references. The chapter on inventory software might have been better omitted; an enormous amount has been written on computerized medical record systems and the nine pages in this book hardly do justice to the subject.

The limp backed format has much to recommend it, more pleasing than a paper back without the high cost of a hard back. The standard of production, especially of the illustrations, is high, the book is a pleasure to possess and can be thoroughly recommended for purchase by individuals and libraries alike.

R. BENTLEY.

National and International Standardization of Radiation Dosimetry. Proceedings of a symposium held at Atlanta, Georgia on December 5–9, 1977, Vol. I, pp. 534, Vol. II, pp. 373 (International Atomic Energy Agency, Vienna, 1978) Vol. I $43.00, Vol. II $31.00.

In December 1977, some 137 participants from 26 countries, including representatives from eight international organizations, gathered in Atlanta under the auspices of the International Atomic Energy Agency, for the presentation of some 65 papers on standardization in radiation dosimetry. The proceedings of this symposium, including any discussion on each paper, have now been published in two volumes, and these provide a clear picture of the state of the art, together with much detailed information.

The first volume contains some 42 contributions devoted to a description of the calibration work performed in (i) national standards laboratories, (ii) secondary standard dosimetry laboratories (currently being established in an increasing number of countries), and (iii) related international activities. The papers relate to both therapeutic and protection-level measurements, and include wide-ranging discussions concerning the dissemination of units. It is evident that the emphasis is on the refinement of established methods, namely ionometric, calorimetric and chemical techniques, rather than the introduction of new concepts.

For convenience, a series of papers relating to absorbed dose determinations are collected together in the second volume, along with eight papers on basic physical aspects, and five contributions devoted to the standardization and calibration of radioactive sources. On the other hand neutron dosimetry has not been included, this topic having been treated at separate symposia.

The general level of the contributions is high, and it is apparent that much progress has been made in the dissemination of radiation units, both nationally and internationally, the uncertainties having been markedly reduced through comparison programmes.

These two volumes should prove a most valuable reference work for anyone engaged in this field of activity.

W. A. JENNINGS.

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Guidelines for the Preparation of Radiopharmaceuticals in Hospitals

Revised 1979 Edition

Special Report No. 11

A Report of a Working Party

Numerous types of diagnostic agents labelled with radio-nuclides are now in routine use for the investigation *in vivo* of human disease. Many of these radiodiagnostic agents contain radio-nuclides of short half-life and for this and other reasons it is necessary to carry out their preparation in hospitals. Little official or other guidance concerning the basic procedures required for the safe preparation of these radiopharmaceuticals has, however, been available. For this reason, following a Seminar on 'Laboratory Facilities and Working Procedures for the Hospital Preparation of Radiopharmaceuticals' held at the Royal Marsden Hospital, Sutton, in October 1974, a working party was set up to prepare some guidelines on this subject. This document comprises the report of this working party; it is concerned not with individual recipes, but with basic principles and procedures. The Report should prove helpful to many of those concerned with the preparation and use of radiopharamceuticals, and it is expected to provoke useful comment and discussion, especially on the extent to which the procedures set down conform to the requirements of the Medicines Act (1968).

In revising the present report it has not been considered necessary to revise any of the original recommendations. However, the opportunity has been taken to amend certain sections to take account of the changes in United Kingdom legislation consequent on the implementation of Article 5(a) of the European Communities Directive (Euratom, 1976) on basic safety standards for health protection against the dangers of ionizing radiation.

Additional references have also been provided, and minor changes made, where necessary to bring the text up-to-date.

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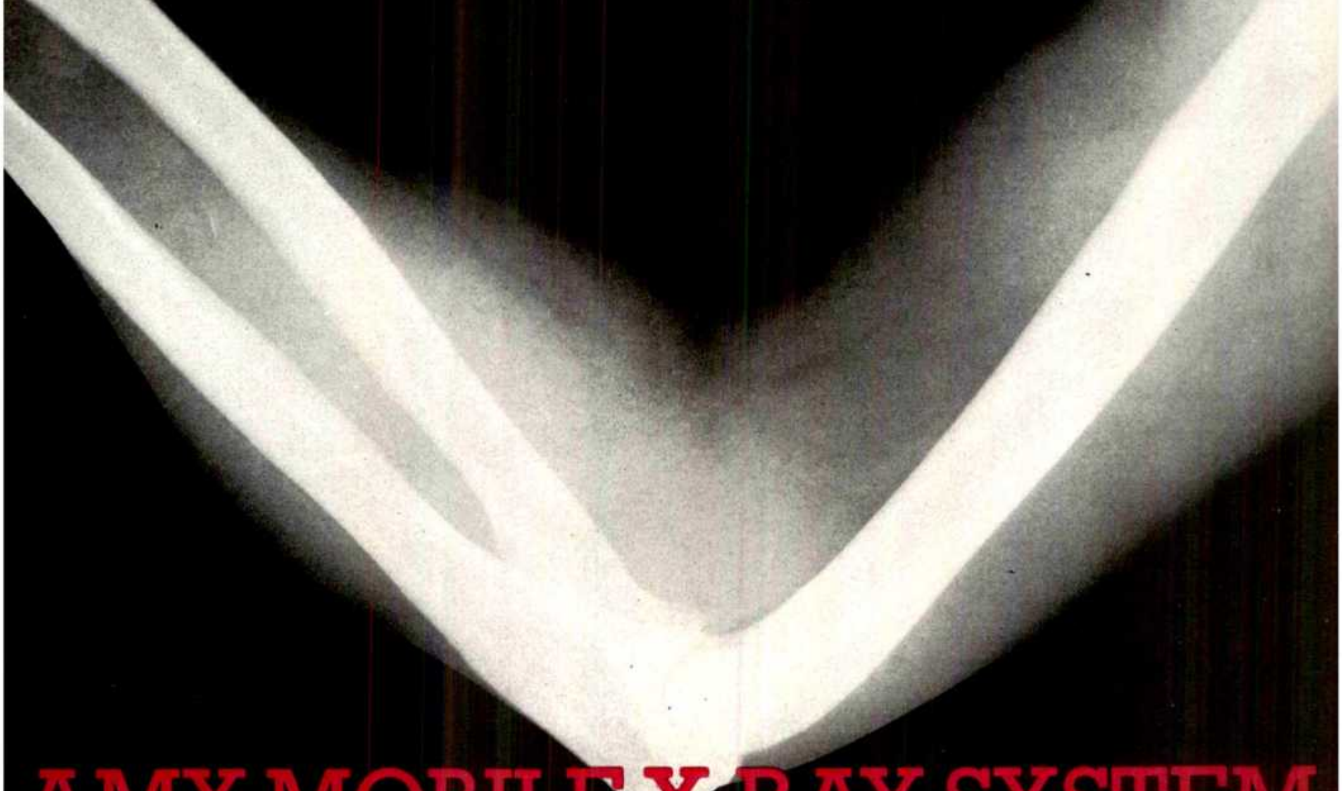

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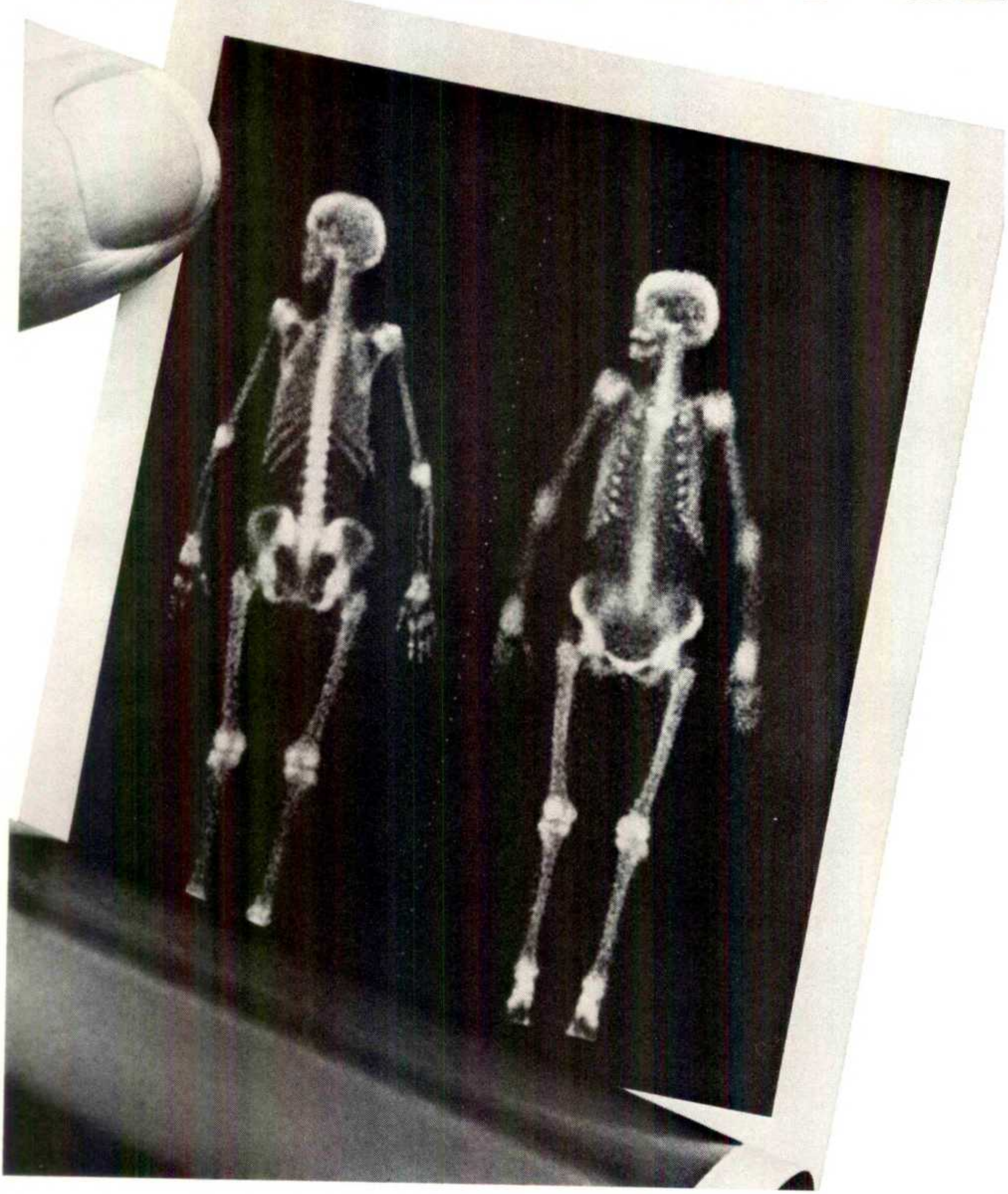

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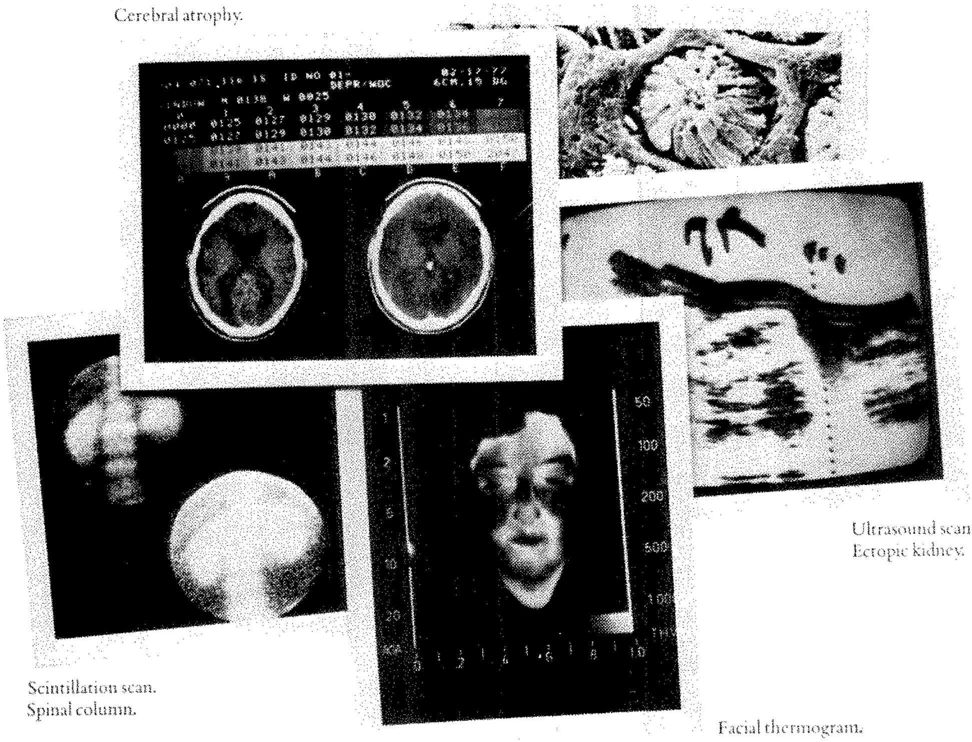
CT scan. Cross-section of brain.
Cerebral atrophy.



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That care is built into the equipment. Concern for the patient's safety goes right back to the earliest stages of design. For that reason the many safety devices do not interfere with the operational freedom – as guards and safety devices introduced as after-thoughts so often do. They ensure that setting misjudgements, or events – such as power failure – beyond the therapist's control cannot harm the patient.

Take the touch-guards (inset). With his oblique view of some movements it is often difficult for the operator to estimate relative positions precisely. The touch-guards ensure that no harm can result from a misjudgement. Their gentle contact stops all movement instantly and the electromagnetic locks of the horizontal table top movements are automatically released until the patient is safely repositioned.

Nor can the patient inadvertently activate switches that might result in injury. For example he cannot operate the table controls because the movement activation switch (inset) underneath is out of his reach.

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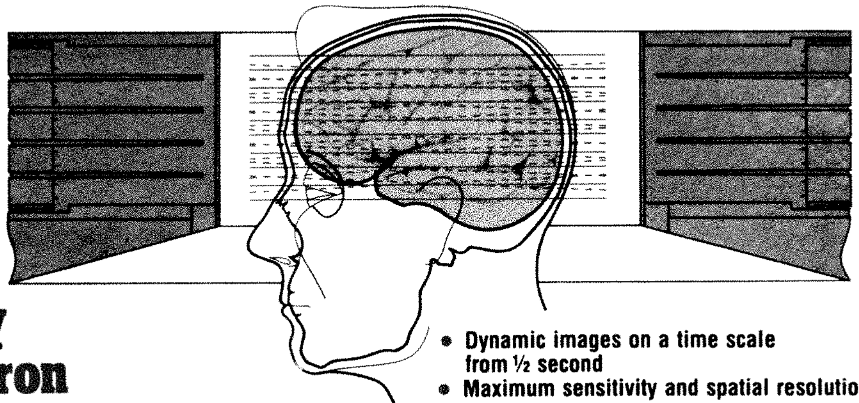

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Specify a Positron Computed Tomography System *to meet your unique research requirements.*

Until recently, the intact human cardiovascular and central nervous systems were not accessible to research scientists for precise quantitative study. The lack of adequate technology to measure "in-vivo" perfusion and metabolism has severely limited the study of these and other dynamic systems. With the introduction of *Multi-slice Positron Tomography* by The Cyclotron Corporation of Berkeley, California, technology in this currently evolving field of research takes a big step forward.

Multi-slice Positron Tomography

Cyclotron's unique Positron Tomograph System represents a promising research tool for non-invasive evaluation of human cerebral and cardiovascular function: Short-lived, positron emitting isotopes (e.g., O^{15}, C^{11}, F^{18}, N^{13}) incorporated into metabolically-active compounds provide a safe "in-vivo" method for monitoring dynamic processes such as perfusion, flow, and metabolism in the human body.

A system to fit the application

One major area of concern among researchers has been finding adequate instrumentation to fulfill particular, and perhaps unique, requirements. Instrumentation requirements are dictated by the research application — any tradeoff between sensitivity, resolution, count rate capability and field of view must be carefully weighed in relation to the application at hand. Accordingly, The Cyclotron Corporation has developed its Multi-slice Positron Tomograph systems in varying configurations to fill a growing number of critical needs. Consider, for example, the Model 4600 (one of the three possible systems indicated in the chart below) in which high resolution and count rate capabilities are paramount system parameters. The Cyclotron Corporation welcomes the opportunity to discuss the research physician's unique interests and to configure a system to meet exacting requirements.

Model Number	Application	Number of Simultaneous Image Planes	Geometric Resolution (x, y, z) (mm FWHM)	Average Sensitivity Per Image Plane*	Maximum Useable System Count Rate**
4500	Body	7	10.0	16000	10^6
4600	Neuro	9	8.5	29000	5×10^5
4650	Neuro	7	5.5	16000	3.8×10^5

*Sensitivity expressed as counts/sec per $\mu Ci/cm^3$ for activity uniformly dispersed in 20 cm diameter, water-filled vessel.

**Defined as the "Trues" rate (counts/sec) at which true counts and random counts are equally abundant in the raw data prior to correction and image reconstruction. Tests conducted with 20 cm diameter water-filled phantom extending well beyond detector shield.

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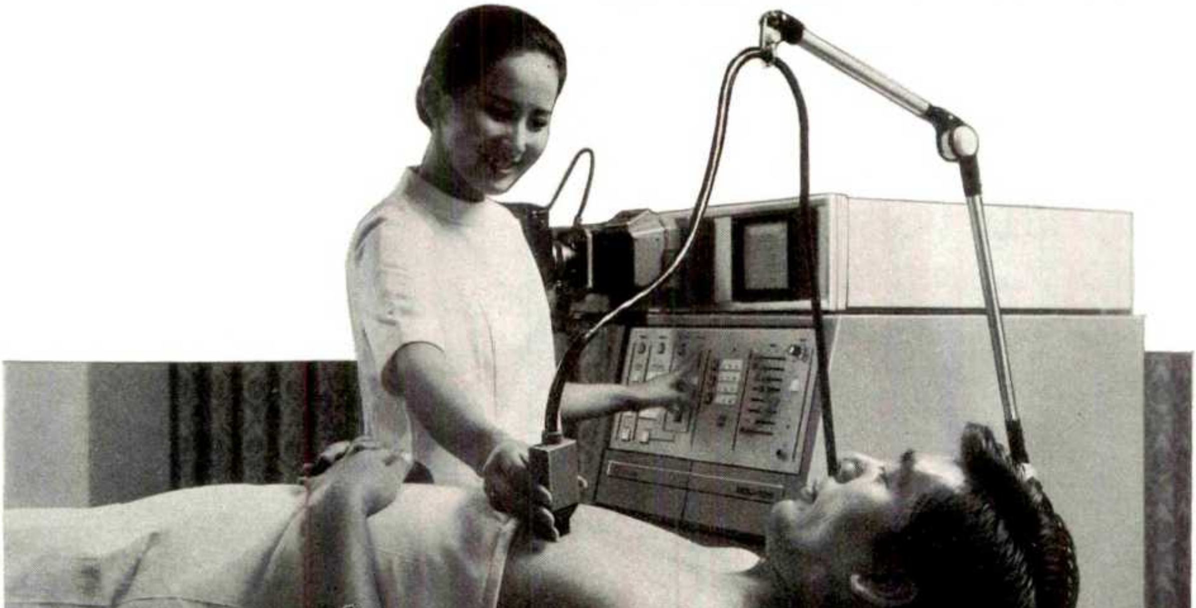

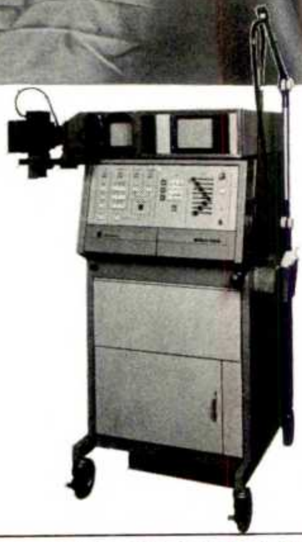

Real-time sector scanning diagnostic ultrasound instruments are now extremely efficient and indispensable for diagnosis of circulatory organs. With the increase in diagnostic accuracy, these instruments are required to be of higher performance and multi-functional. To meet such requirements, Shimadzu has developed an electronic sector scanning diagnostic ultrasound instrument, the SDU-100.

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For full details of the Siemens Angioskop contact: Siemens Limited, Medical Group,
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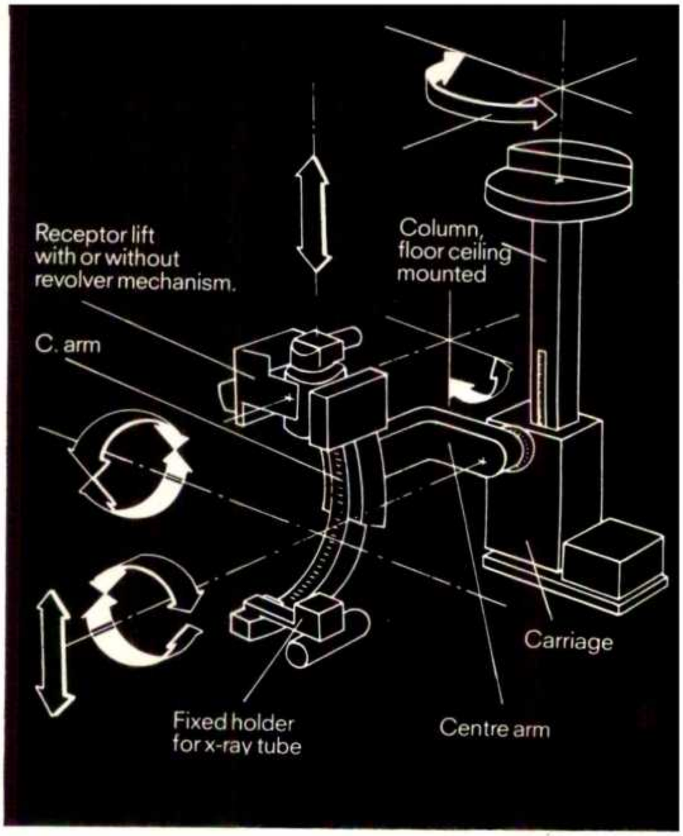
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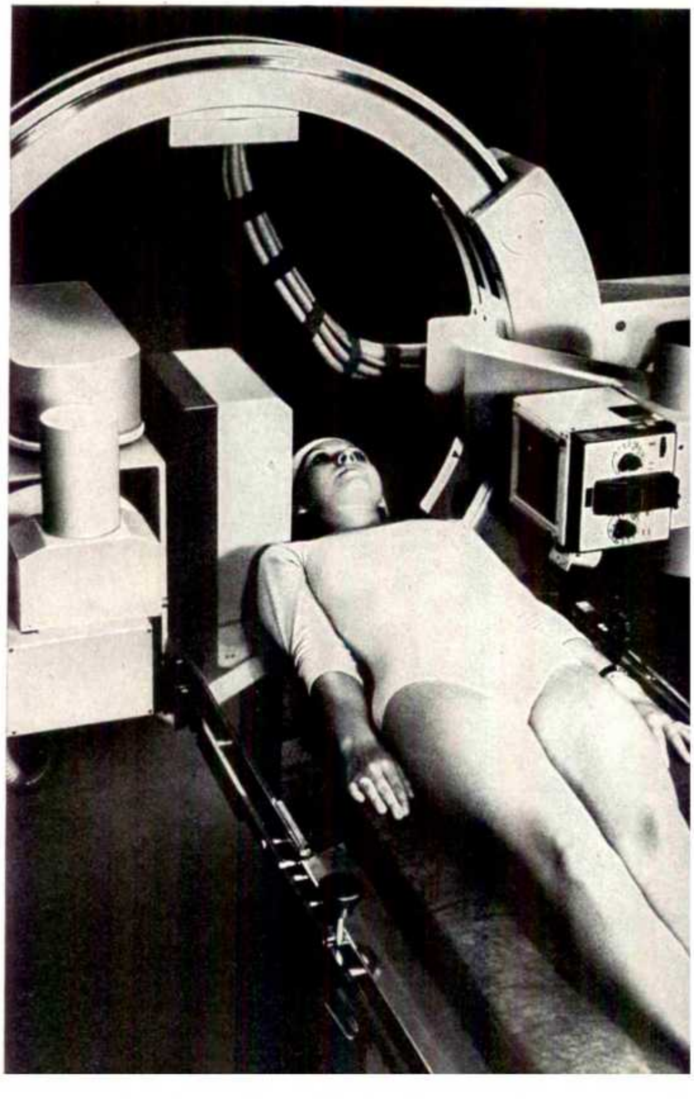

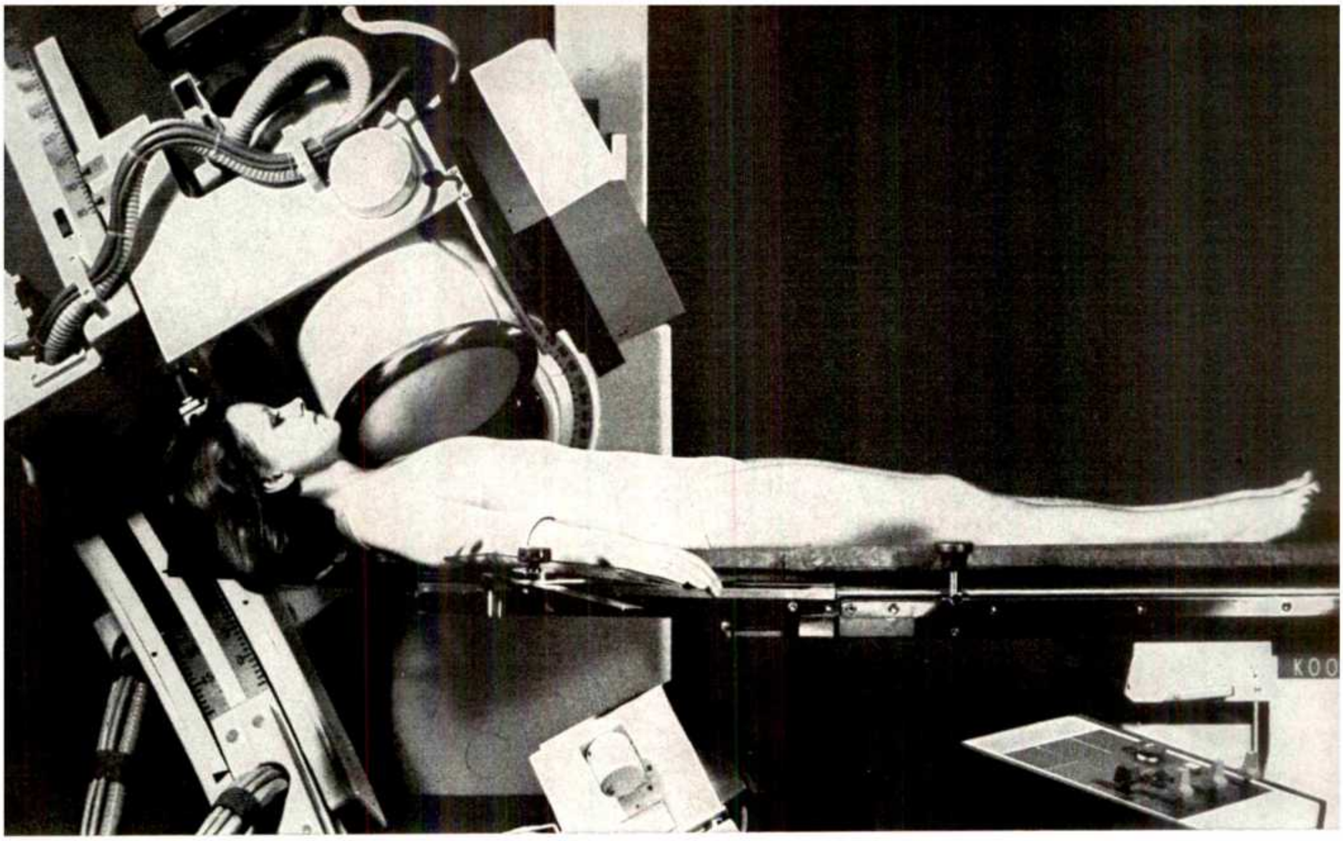
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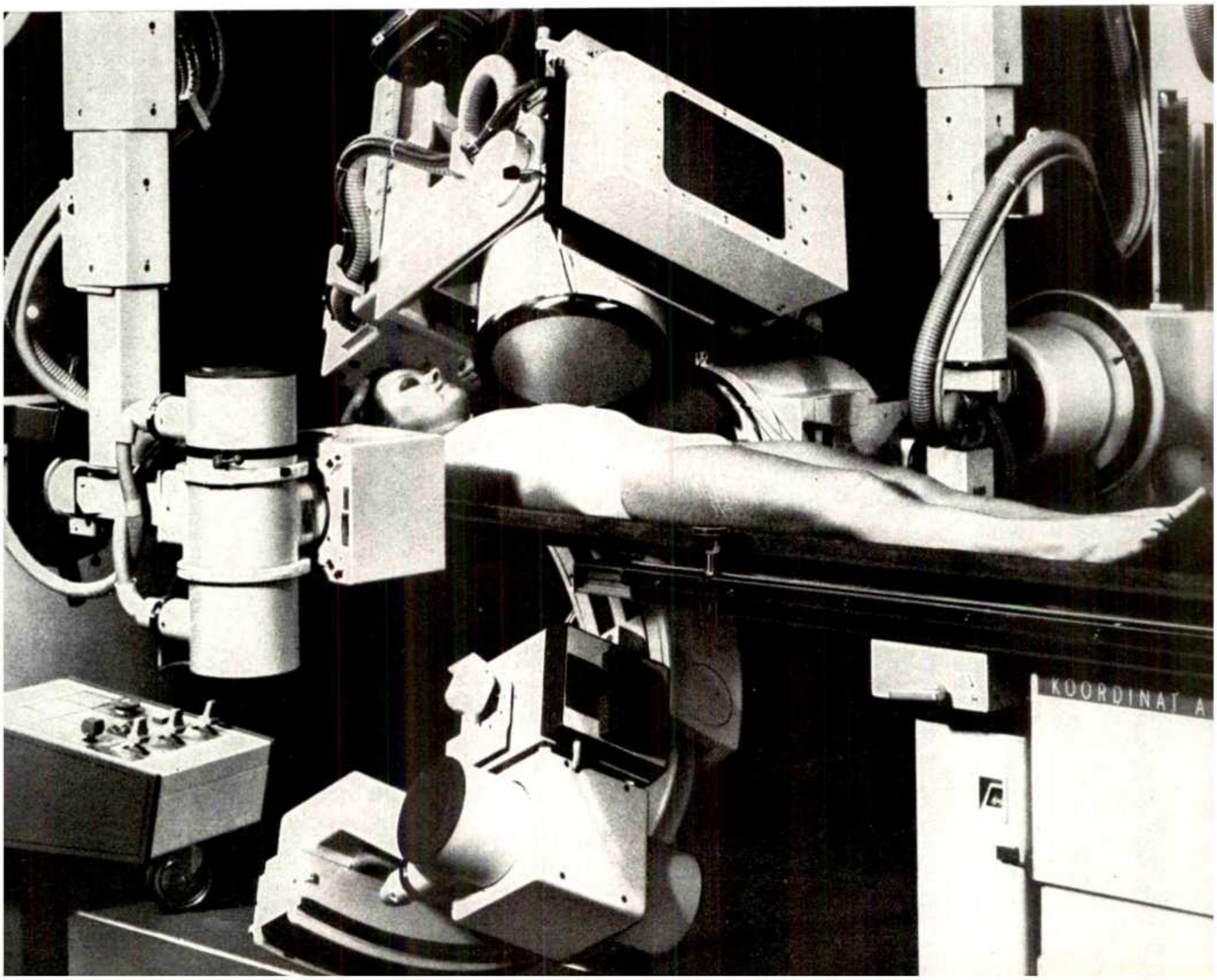
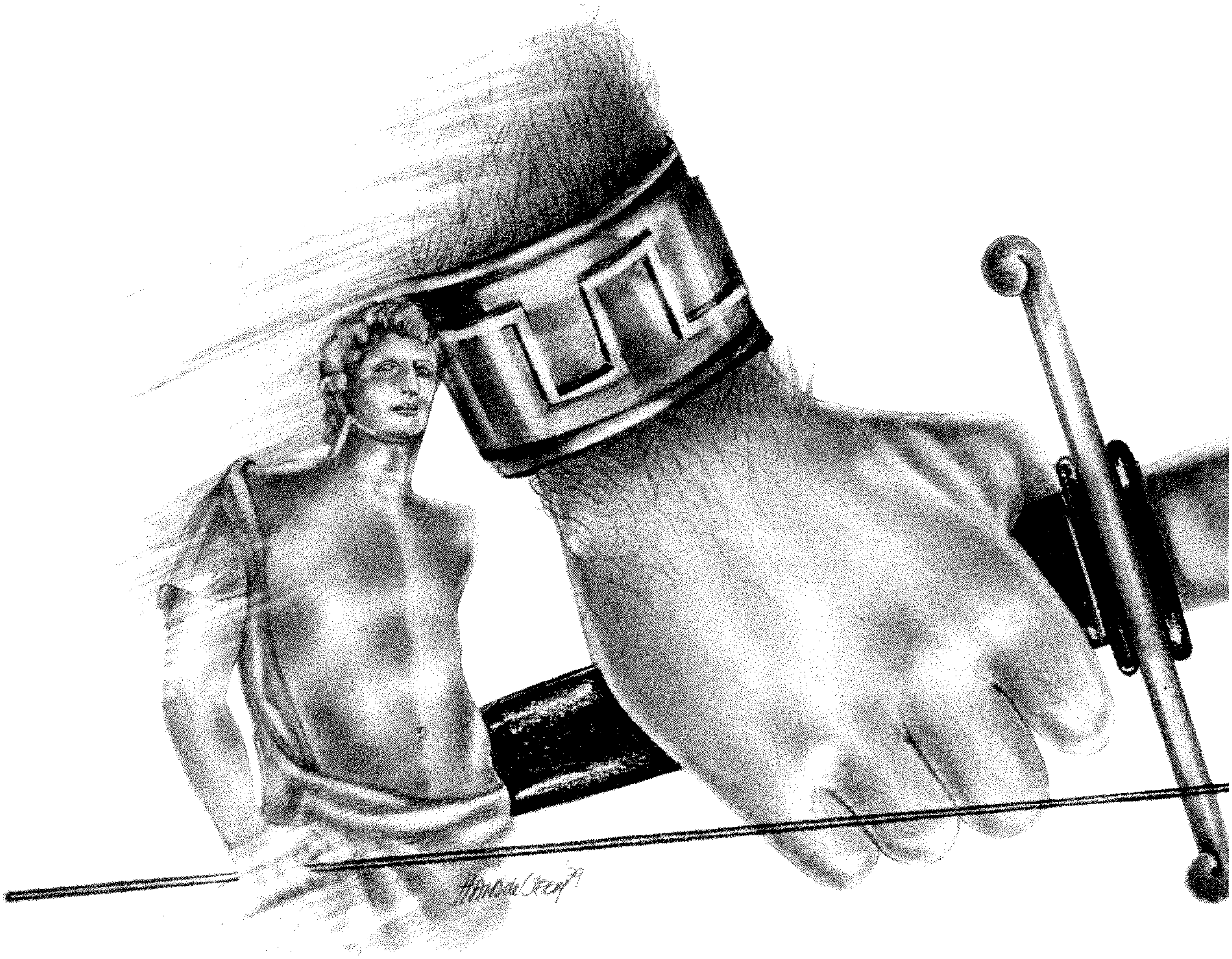

KOORDINAT A

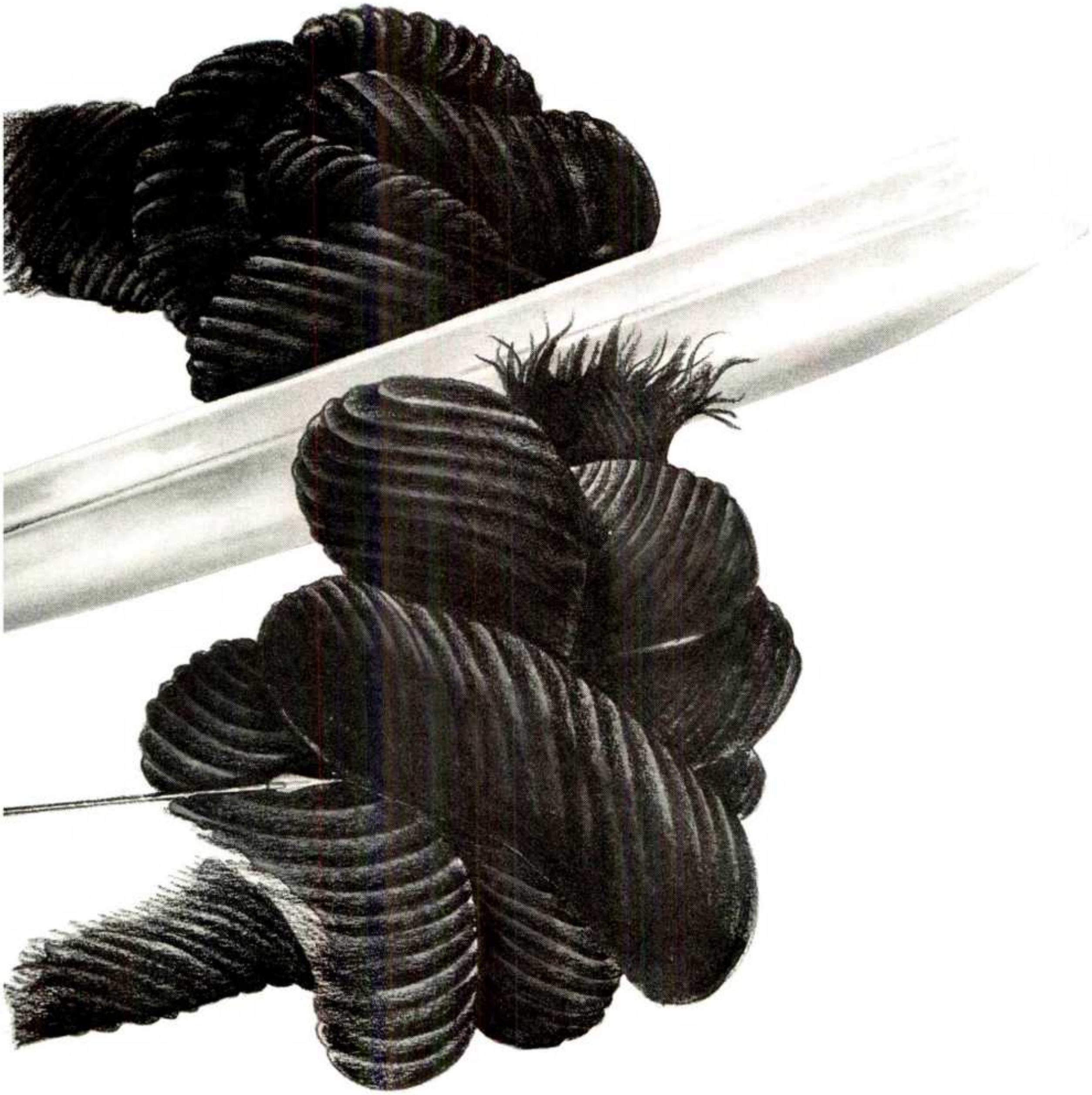
Alexander the Great



so do radiologists

By hacking the Gordian knot Alexander cut through to the heart of the matter.
The rewards were great. So, too, are the rewards for radiologists who opt for sheetfilm for their spotfilm photography: easier viewing, filing and retrieval.
Leading x-ray equipment manufacturers have also seen the light! After all they could not afford to ignore the professional choice of the radiologist. They know that the Oldelft 100 mm sheetfilm camera 'Anodica' is their only guarantee of fail-safe operation of their equipment. That is why they use no other sheetfilm camera; they know better than to try to improve perfection.

knew how to solve problems



Therefore, the 100 mm sheetfilm camera now incorporated in your installation must by sheer definition be the Oldelft Anodica camera (even if it is known by another name, such as Sircam).

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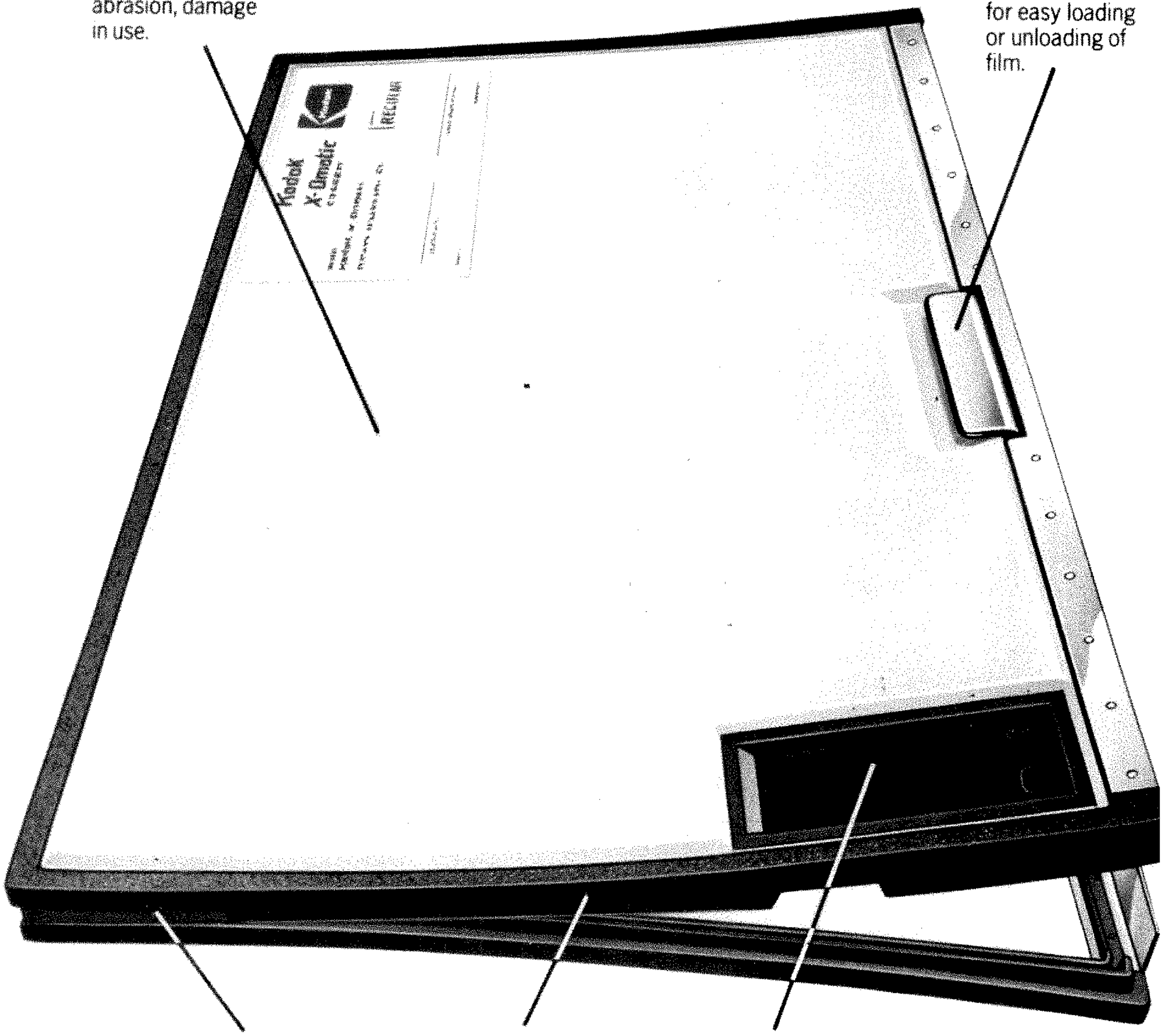

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Curved sides roll out air for total, uniform screen/film contact.

Patient identification window (Model C1 only) used to record patient name, time of exposure, and other essential information helps eliminate error.

that opened the door to roomlight handling

With the KODAK 'X-Omatic' Cassette, Kodak created a remarkable cassette for diagnostic imaging.

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The KODAK 'X-Omatic' Cassette. It's the key to more efficient radiographic imaging.

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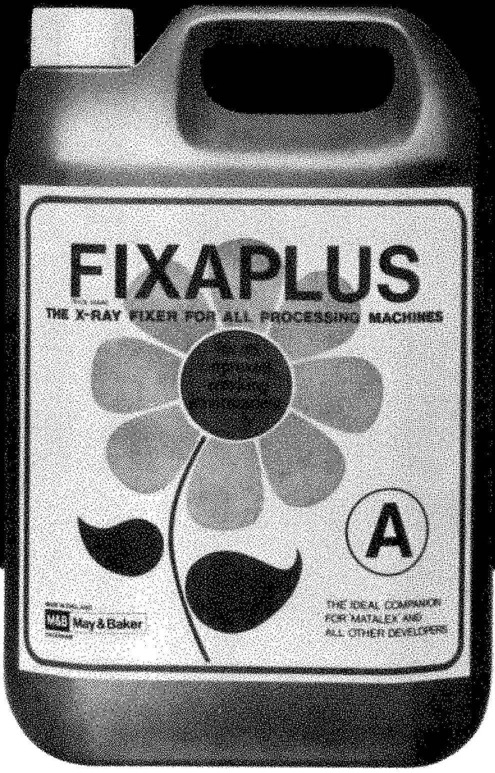
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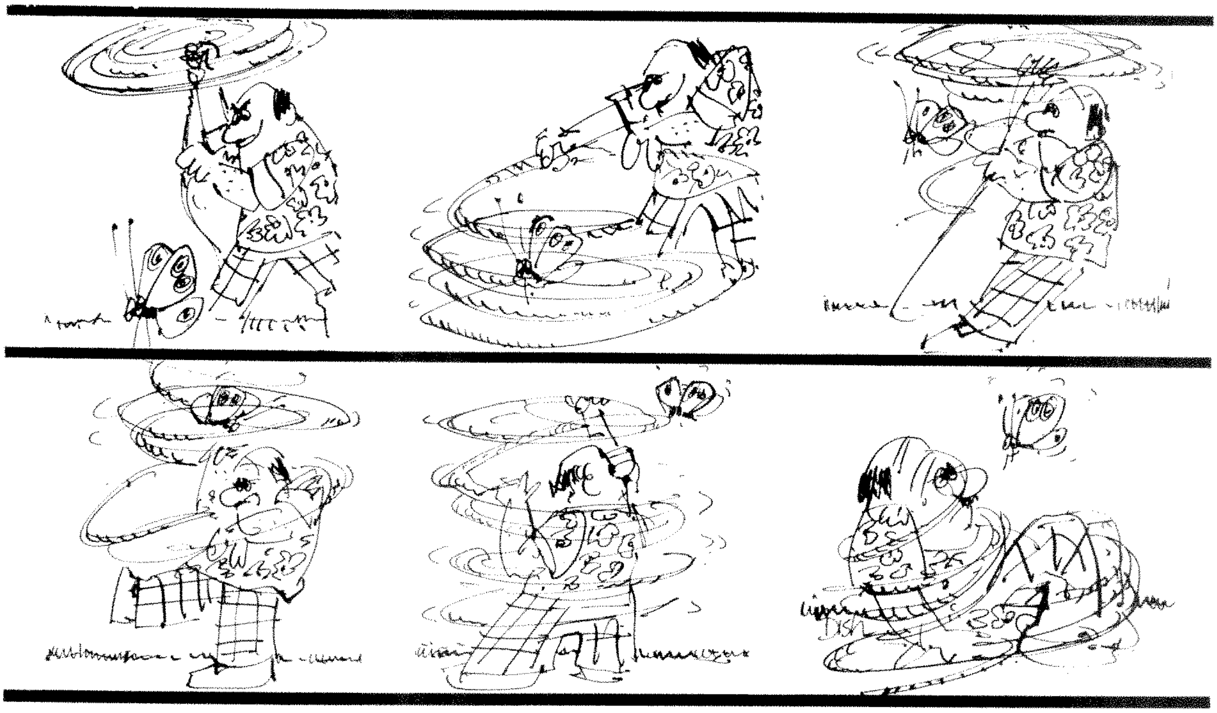

Have you ever tried catching butterflies with a lasso?

In fact it's about as difficult as trying to record grey scale detail on high contrast film.
Until now only high contrast films have been available for recording Nuclear Medicine, C.T. Scan and Ultrasound images even though the latter does contain subtle grey scale detail.
At ILFORD we realized just how difficult this situation could be and so, being experts in image recording, we did something about it.
The results of our research are two new films each designed for its own specific purpose. ILFOSCAN (SP422X) a relatively high contrast film for Nuclear Medicine and C.T. Scanning applications and ILFOSOUND (SP440X) for recording the grey scale detail of Ultrasound.
These two films are the sensible solution to a serious problem. In short, two nets where a lasso wont do.
After all, who enjoys being tangled up in their work.

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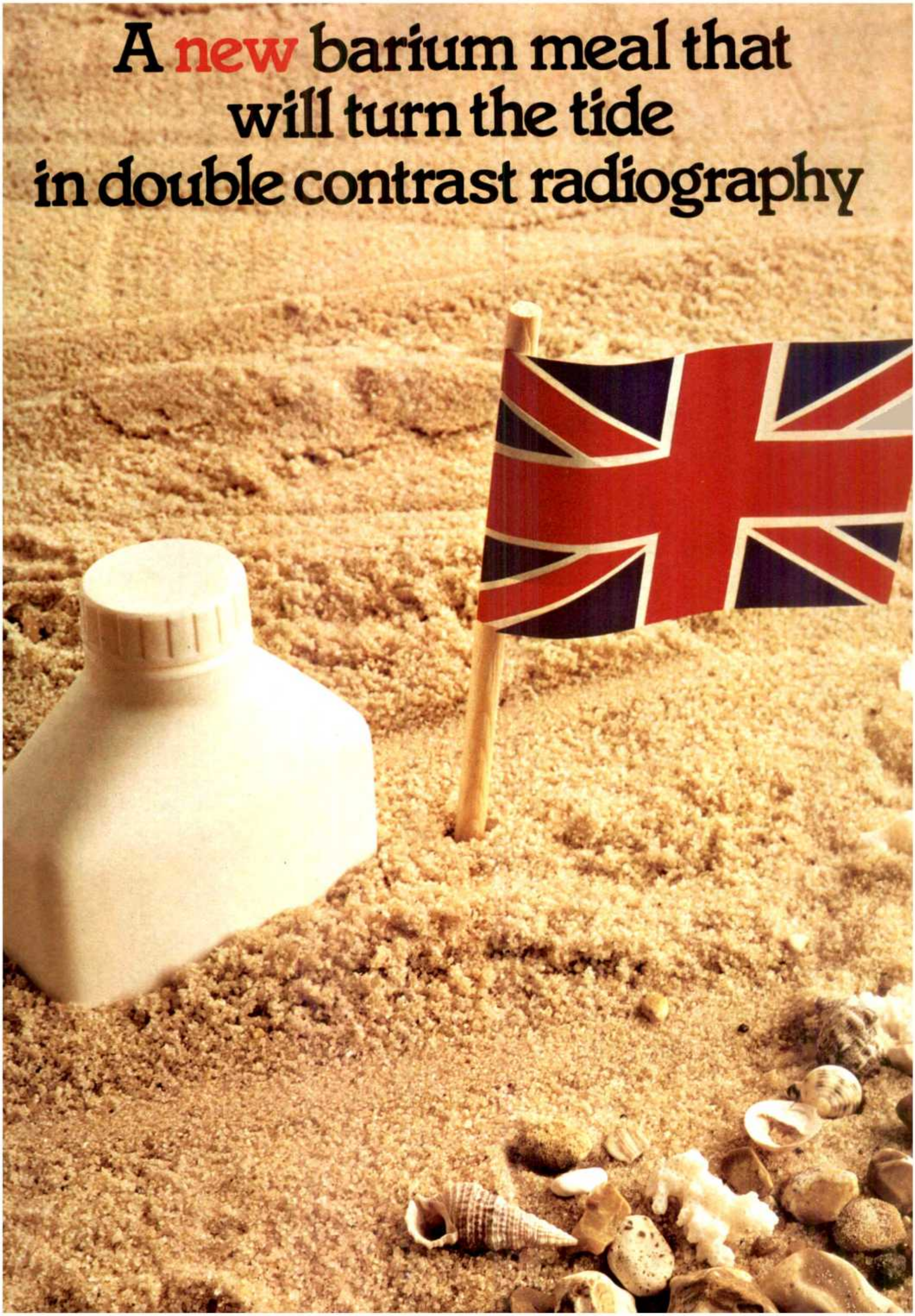
Appointment can either be pensionable or on contract which is renewable on mutual agreement. Successful candidates shall be subjected to conditions of service approved by the Hospital Management Board, which are similar to those obtainable in the Federal Public Service of Nigeria.

Method of Application

Application forms are obtainable from the Office of the Ag. Director of Administration, University of Nigeria Teaching Hospital, P.M.B. 1129, Enugu, Anambra State, Nigeria, to whom completed application forms should be returned not later than 12th October, 1979. Candidates in the United Kingdom can contact our Ag. London Executive Representative for advice and assistance. Her address is: Mrs. E. G. Ojiako, Ag. London Executive Representative, 130 Regent Street (3rd Floor), London WIR 5FE.



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A low viscosity white suspension containing 100% w/v of barium sulphate with a bland taste and particularly suited to the Double Contrast Technique.

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Radiological investigations of the gastro-intestinal tract.

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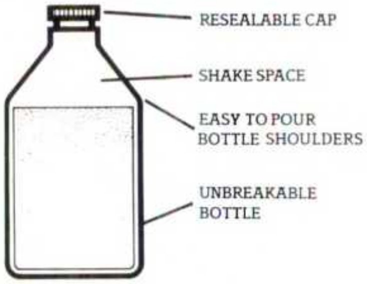

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Shake well before use. Store at room temperature. Do not freeze. A light brown supernatant layer may appear and is quite normal. It will disappear when the bottle is shaken.

Legal Category

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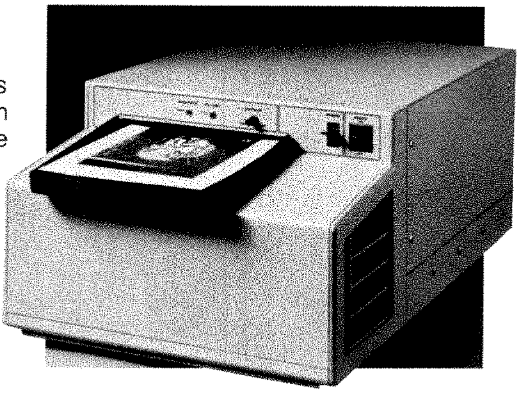

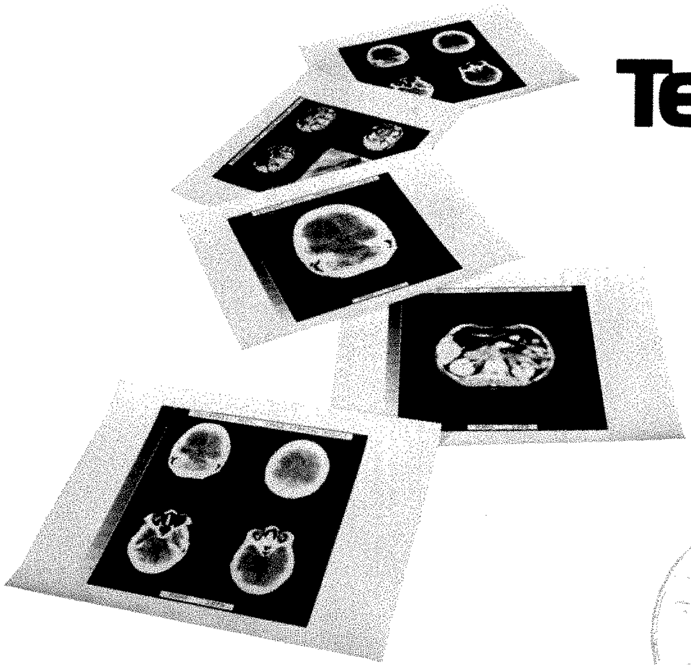

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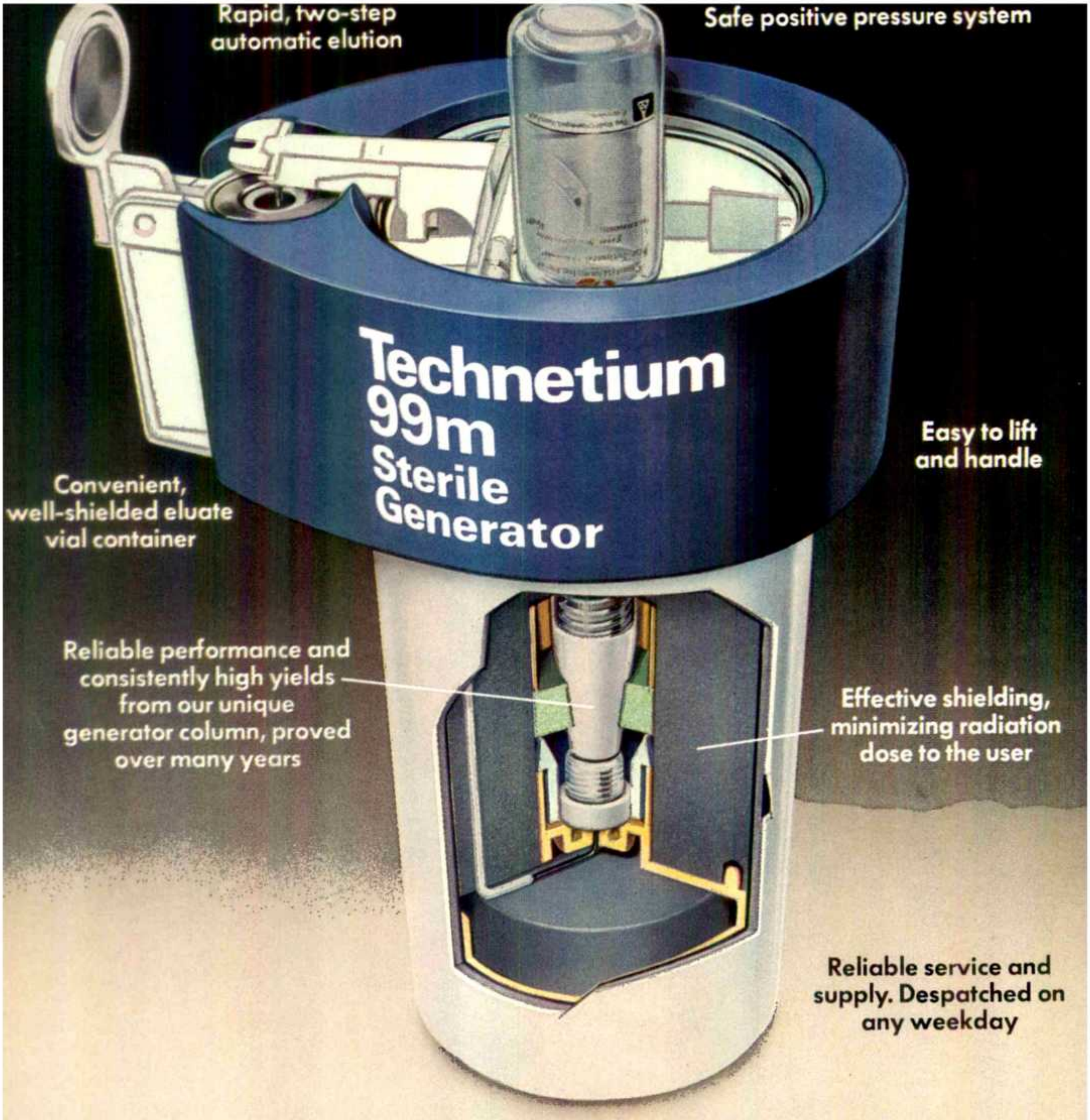
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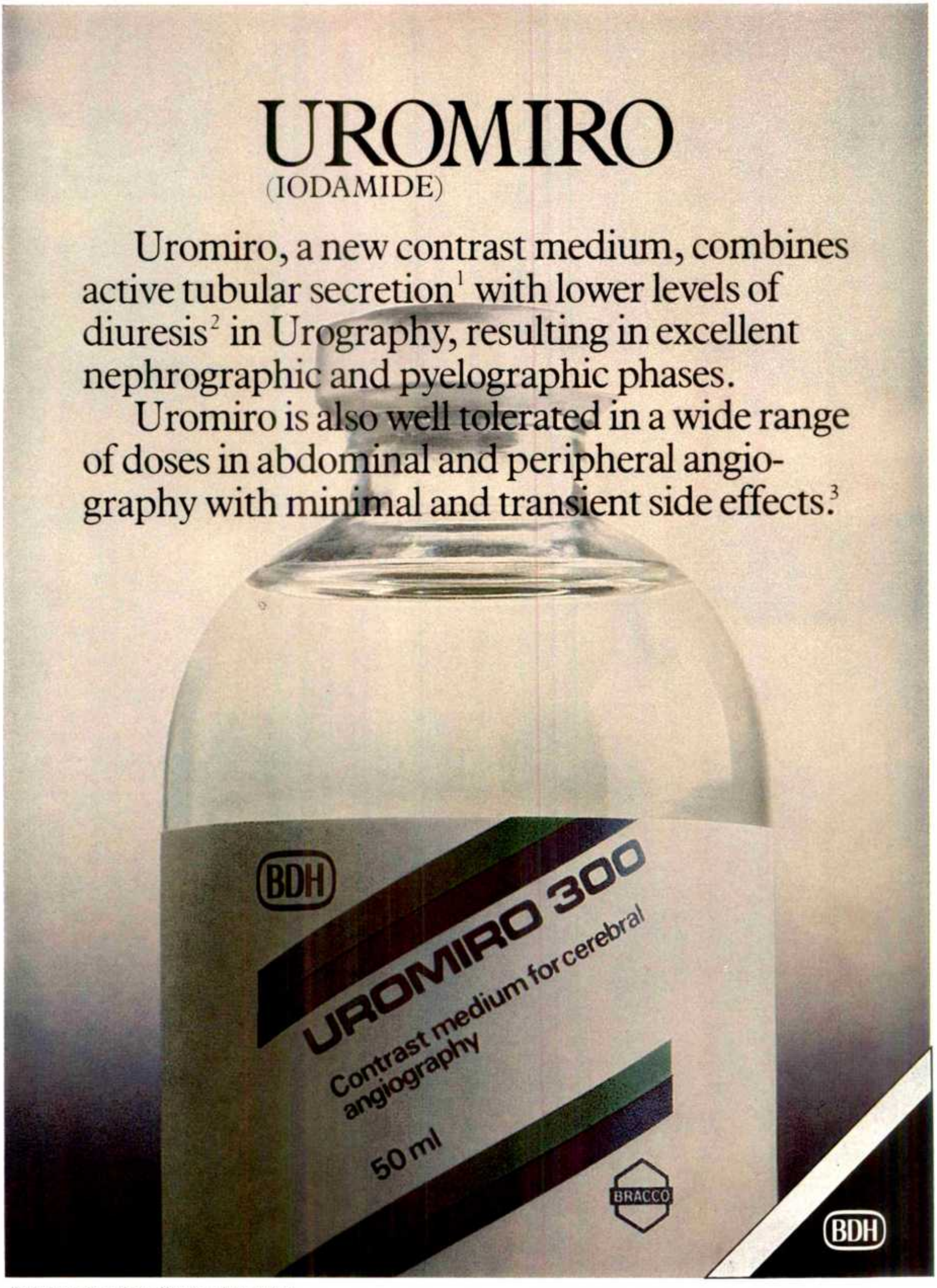

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References 1. Bollerup A.C. et al (1975) European Journal of Clinical Pharmacology, 9, 63–67. 2. Bellizzi, C. (1966) Radiobiologia, Radioterapia et Fisica Medica, 21, 3

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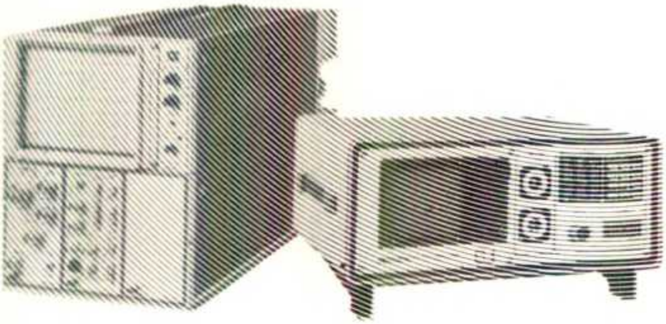

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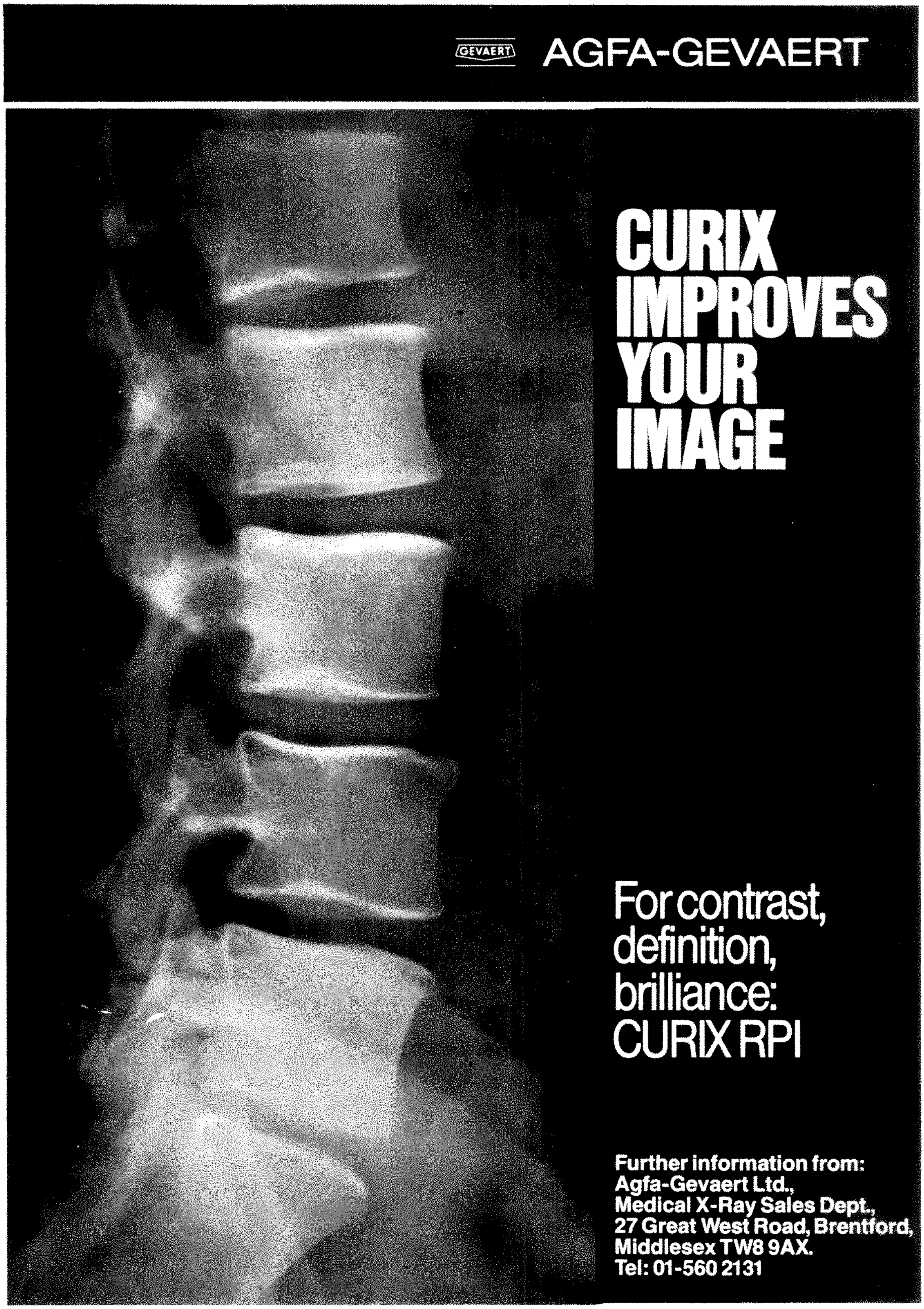

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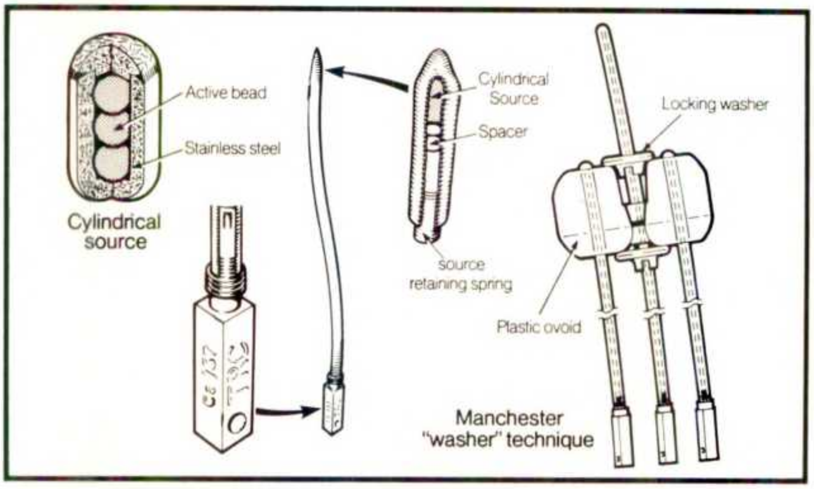

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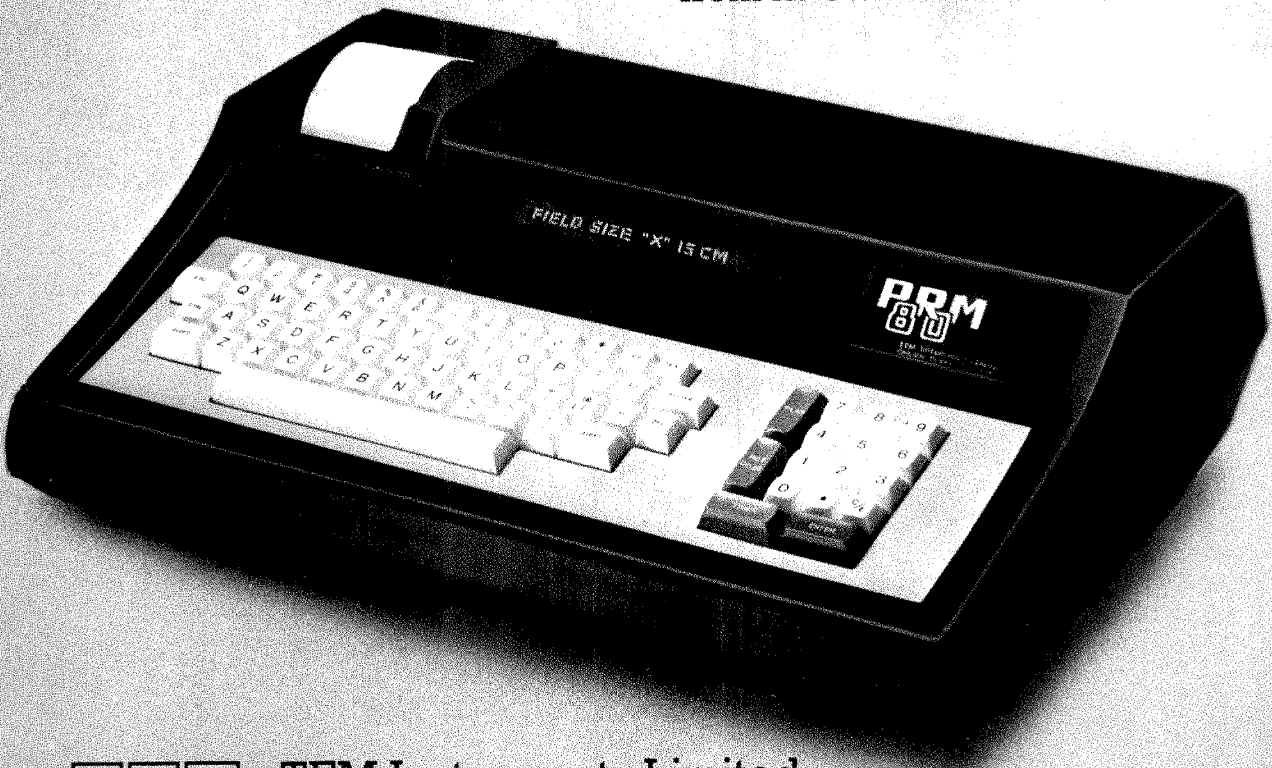

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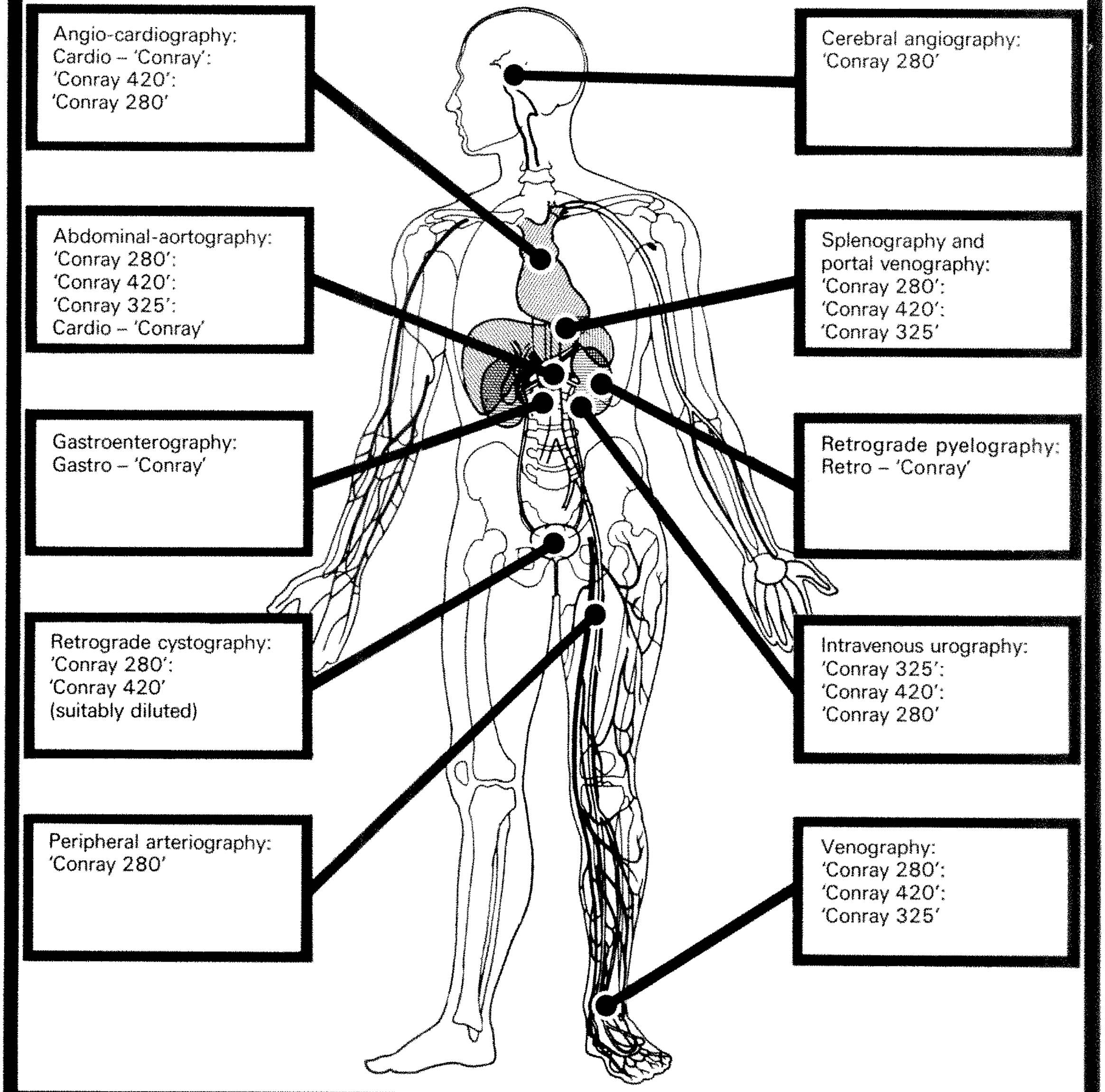

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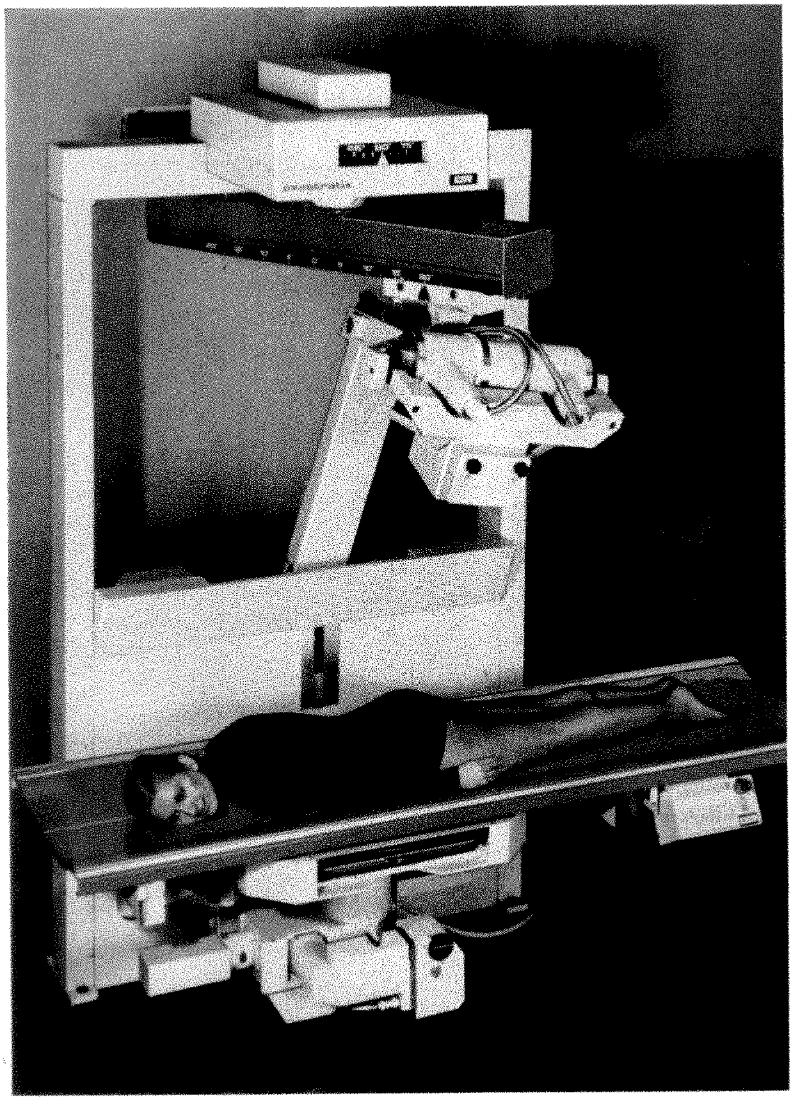

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Review article

Diagnostic ultrasound

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The scope of ultrasound continues to increase very rapidly, especially with the recent introduction of stored grey scale displays and "real time" scanners. Scientific papers, conferences and books on the subject are also proliferating rapidly and the casual observer or busy radiologist can hope to capture but little knowledge of the more recent significant advances and concepts. The purpose of this paper, therefore, is to review the recent literature on diagnostic ultrasound with emphasis on those aspects which the author considers to be most important, relevant or promising. Clearly such a wide ranging review will omit some aspects of the subject and give only passing reference to others but the main topics discussed are those which the average practitioner should find most relevant.

For ease of reference these topics are grouped under a range of headings; thus the busy reader can avoid those sections which do not interest him.

OBSTETRICS

This speciality is the greatest consumer of ultrasound services. Since the early days of diagnostic ultrasound, measurement of the fetal biparietal diameter has been the commonest ultrasound investigation performed. The primary value of this measurement has been in the assessment of gestational age (Campbell and Newman, 1971) and fetal growth (Campbell, 1974).

With a meticulous technique Campbell (1969) achieved a prediction of gestational age with an accuracy of ±8.4 days in 95% of patients. However, Robinson (1973) has shown that measuring the fetal crown-rump length (Fig. 1) between 8 and 12 weeks gestation permits still greater accuracy. Other methods of assessing the gestational age have been advanced, including volume measurement of the gestation sac, but all are less accurate than Robinson's technique.

Ultrasound has also proved valuable in the measurement of patients who present with bleeding in early pregnancy. In our experience 50% of all patients with threatened abortions who were referred for an ultrasound scan had non-viable pregnancies. Fetal viability can be reliably confirmed from 7½ weeks gestational age by detecting the fetal heart (Robinson, 1972) and a wide range of abnormalities may be discovered including complete, incomplete or missed abortions, blighted ova (anembryonic pregnancies) and hydatidiform moles (Fig. 2) (Robinson, 1975). The appearance of a "broken ring"

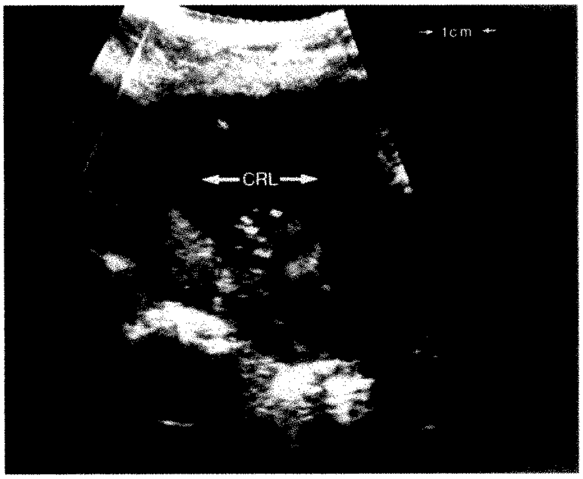

FIG. 1.
A nine week fetus showing the crown-rump length (CRL)

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and low implantation sites have also been described (Donald *et al.*, 1972). These are said to indicate inevitable abortion but the specificity of these signs remain in doubt, the broken ring appearance not being seen so often with a grey scale display. The growth of the fetus and its sac are so rapid in early pregnancy that where doubt exists after one scan a repeat in four or five days will almost invariably confirm or exclude fetal viability.

With the improving resolution of current scanners greater interest has been centred around the early diagnosis of fetal abnormalities. Anencephaly can be diagnosed (with good grey scale equipment) at eight or nine weeks and with older equipment can still be achieved in time to permit therapeutic abortion. Spina bifida has been detected by a number of workers (Campbell *et al.*, 1975) but the high degree of operator expertise that is necessary to achieve or exclude the diagnosis early in pregnancy is only available in a limited number of centres at the present time. Ultrasound cannot therefore be considered a reliable technique for ruling out neural tube defects at the present time, but it is excellent for guiding the amniocentesis needle to a pool of liquor whilst avoiding damage to both the placenta and fetus (Kerenyi and Walker, 1977). This should reduce the incidence of abortion after "genetic amniocentesis".

The ability of ultrasound to display fetal anatomy improves as pregnancy advances and an increasingly wide range of abnormalities have been detected (MacVicar, 1976). Most of these have been incidental findings and of little use in the management of the patients. However, prior knowledge of a severely abnormal fetus may occasionally alter the course taken if premature labour occurs; or may influence the mode of delivery. Ultrasound is also increasingly useful for excluding certain morphological abnormalities such as hydrocephalus, fetal ascites and renal agenesis. The fetal kidneys can reliably be seen from about sixteen weeks gestational age (Fig. 3) and in four patients with severe oligohydramnios we have correctly excluded renal agenesis in three and diagnosed it in one.

Perhaps the second most common reason for obstetric ultrasound examination is to determine the cause of discrepancy between the patient's fundal height and dates. The examination, if performed before 30 weeks gestation, permits confirmation of the gestational age and also enables a diagnosis of multiple pregnancy, hydramnios, fibroid or ovarian cyst to be made.

Strictly speaking, all pregnant patients subjected to an ultrasound scan after about 12–14 weeks gestation should have the placental site noted. A placenta which is well away from the internal os will never become praevia, though many which appear low in the first and second trimesters will be well clear of the lower segment by 32 weeks (King, 1973). King noted this and termed the phenomenon placental migration but it is now generally agreed that the rapid prolongation of the lower uterine segment in the third trimester is the most likely mechanism.

In recent years greater emphasis has been placed on the use of ultrasound as a means of monitoring

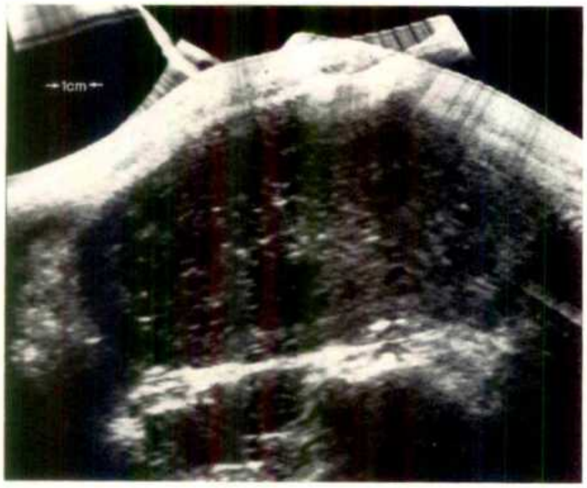

FIG. 2.

Longitudinal scan of uterus showing the typical appearance of a hydatidiform mole.

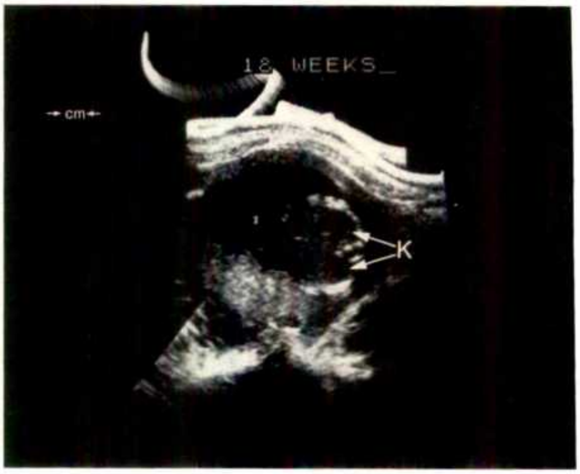

FIG. 3.

Transverse section of a fetal abdomen at 18 weeks. The kidneys (K) are just visible.

fetal growth and function. Campbell (1973) described a technique for measuring fetal urine production by serial volumetric studies of the fetal bladder and over 300 papers have now been written on various aspects of the recording of fetal breathing movements with ultrasound (Marsal, 1977). Whilst both parameters can be shown to become abnormal in severe cases of placental insufficiency neither technique has yet gained clinical acceptance, probably because both require a skilled operator for about one hour for each measurement on each patient.

Much useful information concerning fetal growth can be gained more rapidly by measuring the fetal head and trunk. Biparietal diameter measurements have been widely used for detecting growth retardation in late pregnancy but the physiological "brain sparing" effect in the malnourished fetus ensures that head measurements alone will not detect growth reduction until it becomes severe. We estimate that about 80% of light for dates fetuses have normal head sizes and will not be detected by BPD measurements alone. For this reason many authors have attempted to measure the fetal trunk at a variety of levels. In 1965 Thompson *et al.* observed that abdominal measurements permitted more accurate detection of the small fetus and subsequently measurements of the chest and abdomen diameters, areas or circumferences have been shown to be clinically useful (Campogrande *et al.*, 1977). Most of these authors have tried to predict fetal weight by applying their measurements to a variety of formulae. The derived figures can be no more accurate than the original measurements and the author's preference is for expressing the head and abdomen measurements separately, quoting their positions on graphs of centiles at different gestational ages. There is also little agreement yet as to which measurement is the most satisfactory. Since the liver is affected earlier in growth retardation and exhibits greater changes than any other organ, it seems reasonable to assume that a measurement which most closely reflects liver size (Fig. 4) will be the most sensitive indicator of this condition.

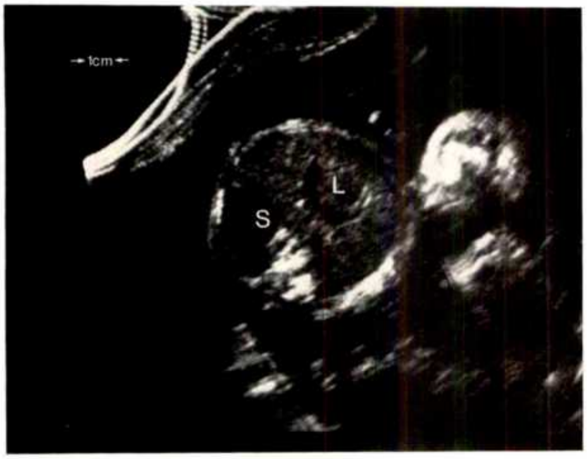

FIG. 4.

Transverse section of a fetal abdomen at 28 weeks, showing the stomach (S) and liver (L). Branches of the portal vein are visible within the liver.

There are two other facets of obstetric ultrasound which have been discussed in the literature recently; (i) the use of "real time" scanners and (ii) the case for routine scanning of every patient. Both are under evaluation at the present time but the continuing developments in real time imaging have produced small, easy to operate machines which provide clinically useful images and measurements in the hands of a comparative novice. Their use in the antenatal booking clinic on a routine basis would permit the confirmation of gestational age and exclusion of multiple or grossly abnormal pregnancies. Patients with blighted ova, moles and anencephalic pregnancies could then be offered early evacuation; and decisions concerning delivery date could be made with greater confidence in patients with irregular cycles or "post pill" conceptions.

GYNAECOLOGY

The use of ultrasound in the complications of early pregnancy has been discussed above and its other main uses in the female pelvis will be presented here. These relate mainly to the differential diagnoses of mass lesions, the assessment of inflammatory disease and its sequelae and the management of patients wearing intrauterine devices.

As at other sites in the body, ultrasound will differentiate solid from cystic lesions with a very high degree of accuracy. With certain provisos the differential diagnosis can often be taken a little further. Statistically speaking, totally solid uterine masses are likely to be myomata. However, these have a very wide spectrum of ultrasound appearances and may vary from densely echogenic (Fig. 5A) to almost echo free (Fig. 5B). Myxomatous or red degeneration can lead to a cystic appearance within a fibroid. The ultrasound appearances of other solid tumours such as ovarian fibromata lie within the range covered by fibroids and such lesions cannot therefore be differentiated at the present time (Lawson and Albarelli, 1977).

Cystic tumours are most often found to be ovarian in origin and it is generally agreed that simple cystic lesions are likely to be benign whilst the more complex lesions with thick septa and solid components

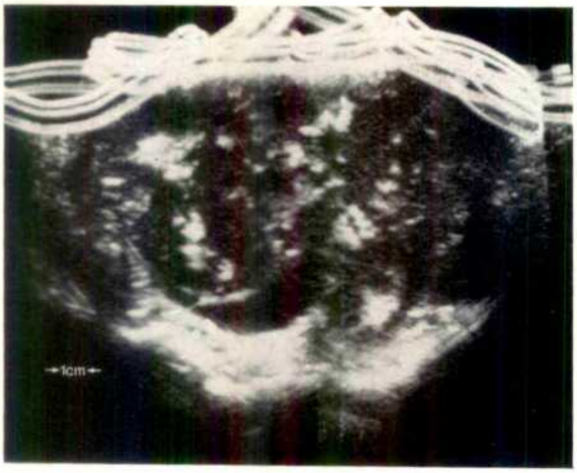

FIG. 5A.
Transverse scan of uterus containing a partly calcified fibroid which returns multiple high level echos.

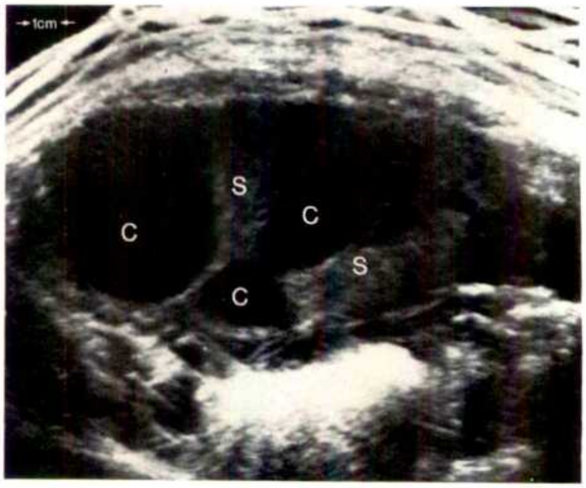

FIG. 6.
Longitudinal scan of pelvis and lower abdomen showing a malignant ovarian tumour containing solid components (S) and cystic spaces (C).

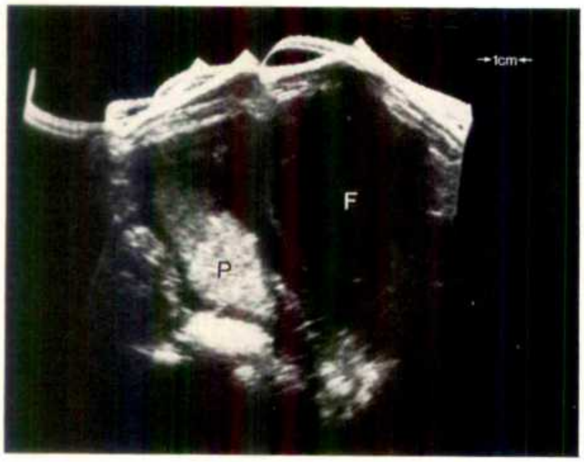

FIG. 5B.
Transverse section of a pregnant uterus containing an almost echo free fibroid (F). Placenta (P).

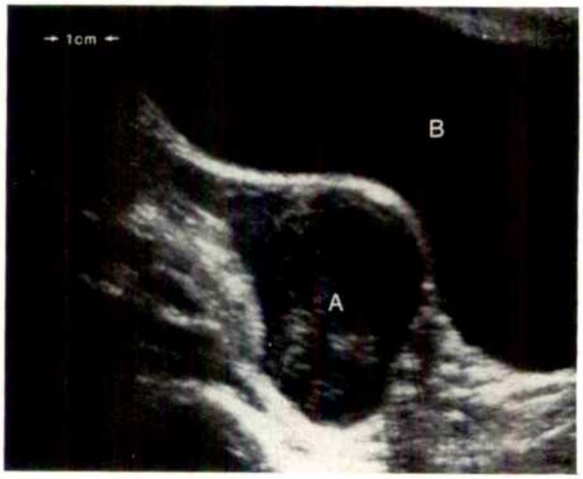

FIG. 7.
Longitudinal scan through a full bladder showing a typical pelvic abscess (A), indenting the bladder (B).

(Fig. 6) are likely to be malignant (Morley and Barnett, 1970; Meire *et al.*, 1978).

Pelvic inflammatory disease may be low grade and not associated with any ultrasonically detectable abnormality. However, obstruction of the fallopian tube may lead to the formation of a hydrosalpinx and this can usually be demonstrated if scanned through a full bladder (Sample, 1977). Acute pelvic inflammation may be associated with abscess formation and the grey scale ultrasound appearance of this condition is fairly characteristic (Fig. 7). The progress or resolution of the condition can be monitored by serial scans.

A few authors have recently found it possible to display the normal ovaries; and the developing follicle now lies within the resolving power of modern scanners (Hackeler, 1978). Intra-uterine contraceptive devices can invariably be detected by ultrasound if correctly located within the uterine cavity (Wittman and Chow, 1976). The patient is able to confirm retention of the device by palpating the attached threads, but if these become impalpable an alternative means of reassuring her and her doctor may be needed. Most devices are radio-opaque and an X-ray film will confirm their presence within the patient. Ultrasound will confirm their presence within the uterus and should ideally be done first. If neither a pregnancy nor an IUCD are detected by ultrasound then radiography can be performed to see if the device lies outside the uterus.

GASTROENTEROLOGY

From an ultrasound standpoint the investigation of this system is essentially confined to examinations of the liver, gall-bladder and pancreas. Tumours of the stomach and colon can be detected by ultrasound scanning but the appearances of such lesions are not specific. At the present time ultrasound cannot hope to compete with contrast radiology in this field. The recording of gastric motility has also been reported (Bateman *et al.*, 1977) but the clinical value of this technique remains to be proven. I will therefore review the role of ultrasound in each of the above gastrointestinal appendages in turn and conclude with an analysis of its use in the jaundiced patient.

Liver

It is now accepted that a grey scale display is essential for imaging the liver. Modern scanners are able to resolve the portal and hepatic venous radicles and can reliably distinguish one from the other (Carlsen and Filly, 1976). The bile ducts, however, remain just below the limits of resolution at present unless they are dilated (Lawson, 1977). This will be discussed below under the section concerning investigation of the jaundiced patient. In the majority of cases ultrasound scanning of the liver will be aimed at detecting parenchymal disease. This may be either diffuse or focal disease and, in general, the latter is far more easily detected as the adjacent normal liver can be contrasted with the abnormal areas. Operator technique, choice of transducer, equipment control settings and patient physique will all affect the general echo pattern obtained from the liver, making standardization of the echo appearances virtually impossible at the present time. However, with experience one can learn to recognize the more obviously altered echo patterns which may occur in diffuse diseases. In general these are either a diffuse increase in echo amplitudes, often with excessive attenuation of sound (Fig. 8), or a reduction in echo production. The author with the greatest experience of this type of disorder is probably Taylor and he reports the presence of increased echo amplitudes with increased attenuation in established cirrhosis. He also suggests that increased amplitudes may be seen in chronic venous congestion, fatty liver and chronic active hepatitis (Taylor *et al.*, 1976). This opinion is supported by the recent work of Joseph *et al.* (1979). Generalized reduction in amplitudes may be seen in acute venous congestion, diffuse malignant infiltrations; and apparently in the benign cellular infiltrations sometimes seen in patients with lymphoma. Unfortunately, the appearance of all these disorders can be mimicked in normal patients if the equipment controls are incorrectly adjusted.

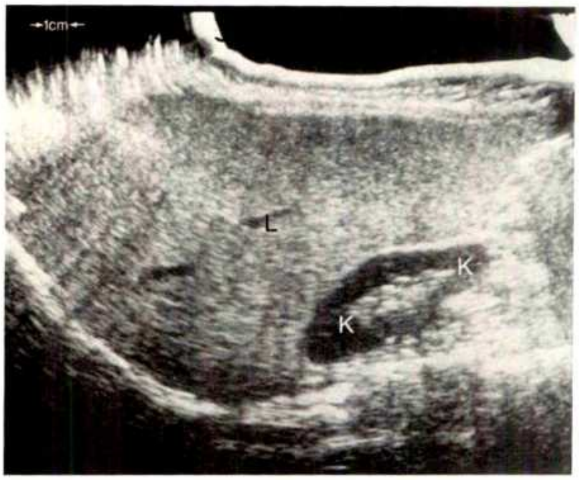

FIG. 8.

Longitudinal scan of right lobe of liver (L) and right kidney (K). The liver is enlarged and contains increased echo amplitudes typical of cirrhosis.

Focal liver disease is easier to detect, patients usually being examined for one of two reasons: firstly for further evaluation of a known or suspected mass, often an isotopically cold area, or secondly for the exclusion of metastases in patients with known or suspected primary malignancy.

Grey scale ultrasound produces a wide range of appearances from the different types of focal disease and many of these permit a very narrow differential diagnosis to be achieved. Experience is still rather limited, however, and a still wider range of specific patterns will undoubtedly be described within the next few years. For convenience I have divided focal disease into benign and malignant and will describe the findings in benign disease first.

Perhaps the commonest benign lesion is the simple cyst. As at other sites liver cysts appear as clearly circumscribed spherical lesions with a thin wall and no internal echoes. They may be almost any size, single or multiple, and when found the kidneys should also be examined.

Hydatid cysts are readily demonstrated and may have lammellated walls or contain debris or daughter cysts. Old inactive cysts may appear entirely simple and be indistinguishable from developmental cysts.

They are, of course, frequently multiple and may be associated with cysts at many other sites.

Hepatic abscesses are readily demonstrated by ultrasound scanning. Their appearance will alter according to the type of abscess and the stage in its evolution at which it is scanned. In general, they have thick irregular walls and contain much debris (Albertson and Leopold, 1977). The proportion of clear fluid varies widely and in our experience is often greatest in amoebic abscesses. Ultrasound is ideal for monitoring the progress of an abscess and for guiding the aspiration needle (Smith and Bartrum, 1974).

Solid benign lesions are unusual. Those whose ultrasound appearances have been described to date include vascular malformation and benign nodular hyperplasia. Cavernous or venous malformations appear as multiple loculated cysts and often appear multilobulated. Capillary lesions return very densely packed high level echoes and are very clearly defined. They may calcify and cause acoustic shadowing. Almost all vascular malformations will be incidental findings and may be multiple.

Benign nodular hyperplasia (benign hepatic adenoma) is a very rare condition which may be associated with consumption of oral contraceptives. The ultrasound appearance is of a complex mass with clearly defined, often lobulated, borders and multiple echogenic and echo free spaces. This is an unusual pattern, though experience is still too limited to say how specific it is.

Primary malignant hepatomas are also uncommon in most centres but it is already clear that their acoustic properties are protean. A hepatoma may appear as a dense echogenic area, a mixed pattern, or be predominantly cystic. There is no reliable indicator as to the diagnosis on ultrasound criteria alone.

Metastases are also extremely variable in their appearances but there is at least some correlation between the ultrasound pattern and tissue type (Meire, 1977). Whilst results quoted from different centres vary widely, it seems that there is general agreement that echogenic lesions (Fig. 9) generally result from gastrointestinal primaries whereas echo poor metastases are most commonly due to breast primaries (Smith *et al.*, 1976). There are, however, no hard and fast rules and almost any primary may give an echo poor secondary in the liver. Truly cystic metastases (Fig. 10) are seen from cystadeno-carcinoma of the ovary and pancreas and also from renal, gastric and occasionally colonic lesions. Complex "target" or "bull's eye" lesions have also been described and are possibly more common from oat cell carcinoma of the bronchus (Green *et al.*, 1977).

The accuracy with which ultrasound will detect liver metastases varies according to the diligence with which they are sought. If the equipment controls are not optimally adjusted then the relatively subtle changes in echo amplitudes produced by some metastases may be overlooked. Similarly, if scans are taken at widely spaced intervals across the liver lesions several centimetres in diameter may be entirely overlooked. However, if the liver is surveyed methodically with closely spaced scans obtained on correctly adjusted equipment using the technique

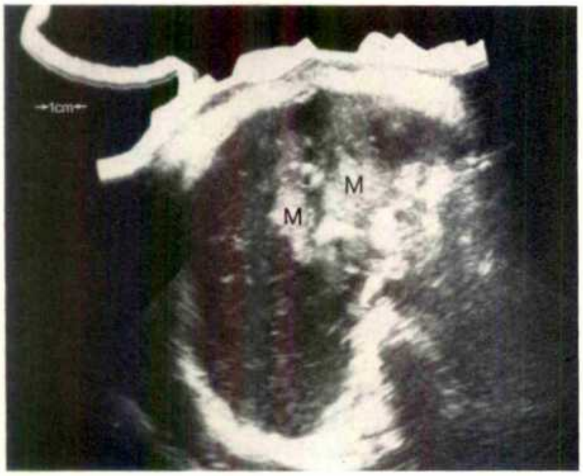

FIG. 9.

Transverse scan of liver showing echogenic metastases (M) from a carcinoma of the colon.

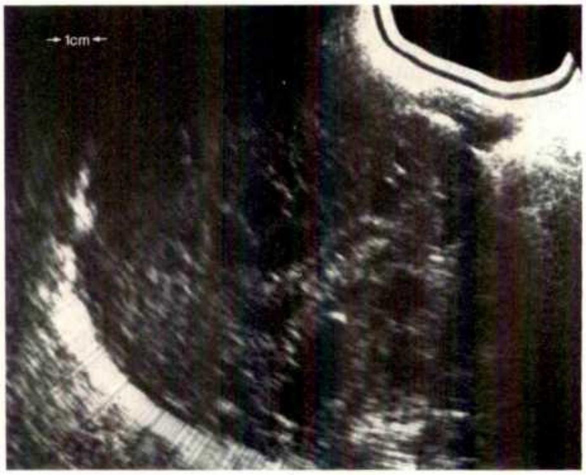

FIG. 10.

Longitudinal scan of liver containing multiple cystic metastases from carcinoma of the oesophagus.

described by Taylor and Hill (1975) it is likely that over 90% of lesions greater than one centimetre in diameter will be detected. Technically inadequate or false negative results will be obtained in patients with high diaphragms, a low costal margin or moderately severe obesity. It also seems clear that a significant minority of liver metastases return echo amplitudes which are indistinguishable from those of normal liver, and these lesions are therefore undetectable by current ultrasound equipment. The exact incidence of such lesions is difficult to determine, but our own experience suggests that they constitute approximately 3% of all cases of liver metastases.

Several authors have shown the feasibility of using ultrasound to estimate the liver volume (Carr *et al.*, 1976). The measurements are rather time consuming, their accuracy is open to question and they are not in wide clinical use.

Gall-bladder

The success rate for detecting the gall-bladder varies enormously from centre to centre. Experienced operators achieve about 90% success (Arnon and Rosenquist, 1976). A wide range of abnormalities have now been described but most are of limited diagnostic value. The prime function of ultrasound imaging of the gall-bladder is in the diagnosis of calculous disease. So long as there is some fluid bile within the gall-bladder, calculi can be detected with a very high degree of accuracy (Anderson and Harned, 1977). The majority of calculi cast acoustic shadows and this may aid in their detection, particularly if little bile is present (Fig. 11). The size and shape of the gall-bladder can be measured and changes in size after a fatty meal can readily be demonstrated, and may help to confirm functional normality. Most authors agree that ultrasound cholecystography does not replace the radiographic examination but that the two are complementary (Leopold *et al.*, 1976). Ultrasound may be of diagnostic value when oral cholecystography has failed. The findings in acute cholecystitis are, as yet, uncertain but thickening of the gall-bladder wall has been shown in this condition and our own observations confirm this finding.

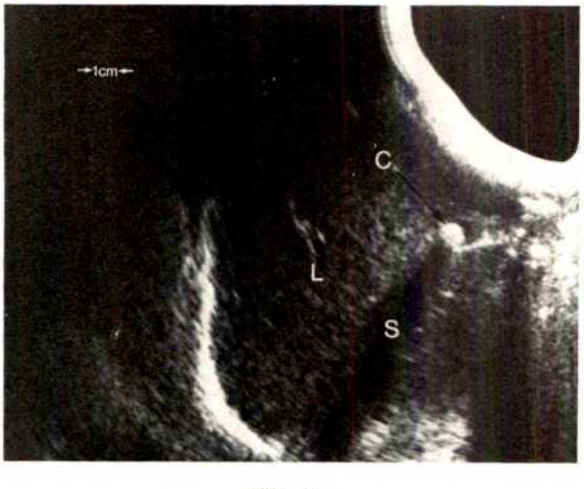

FIG. 11.

Right parasagittal scan. There is a calculus (C) in a small gall-bladder. The acoustic shadow (S) helps to indicate the presence of the calculus. Liver (L).

Pancreas

This is one of the most difficult organs for most operators to visualize. Until recently all authors regarded the normal pancreas as being invisible to ultrasound scanning (Haber *et al.*, 1976). Grey scale display and careful attention to technique now permit success for visualizing the head and body in 80–90% of patients (Haber *et al.*, 1976). The normal gland returns echoes of amplitude similar to or a little above that of normal liver, and the normal duct may occasionally be seen but is more likely to be seen if dilated (Gosink and Leopold, 1978). Diffuse disease is generally inflammatory and when acute causes a generalized reduction in echo amplitudes and concurrent enlargement of the gland (Doust and Pearce, 1976). Pseudocyst formation can be detected with nearly 100% accuracy (Duncan *et al.*, 1976). Chronic pancreatitis results in areas of fibrosis, fat replacement and calcification. The ultrasound appearance is thus also very heterogeneous, the balance between high and low level echoes depending upon the stage and severity of the disease (Doust, 1975). Established chronic pancreatitis produces an amorphous area of irregular very high amplitude echoes which are fairly characteristic (Fig. 12). Conversely, relatively mild forms of chronic pancreatitis may produce no detectable change on ultrasound examination and a normal ultrasound scan does not therefore exclude the diagnosis of chronic pancreatitis. The value of ultrasound in chronic pancreatitis is perhaps further reduced by the occasional similarity between the appearances produced by this disease and those resulting from pancreatic carcinoma.

Pancreatic carcinoma is usually a focal lesion and a mass is generally present at the time of diagnosis. The background of echoes in the tumour is generally lower than that of normal pancreas though local areas of high amplitude may also be present (Wright *et al.*, 1979). Unfortunately, the appearance may be

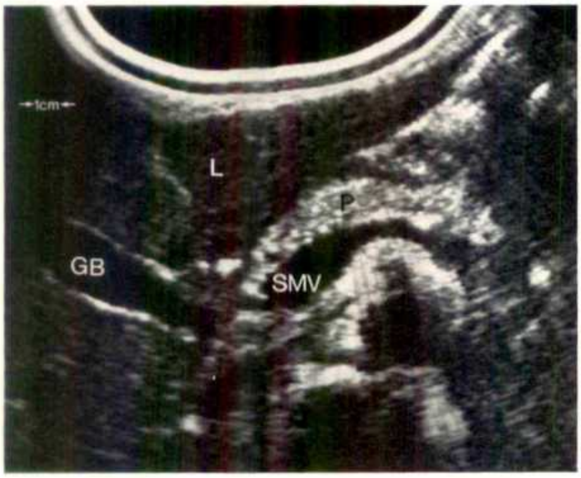

FIG. 12.
Transverse scan of the upper abdomen. The pancreas (P) contains irregular high amplitude echoes typical of chronic pancreatitis. Liver (L). Gall-bladder (GB). Superior mesenteric vein (SMV).

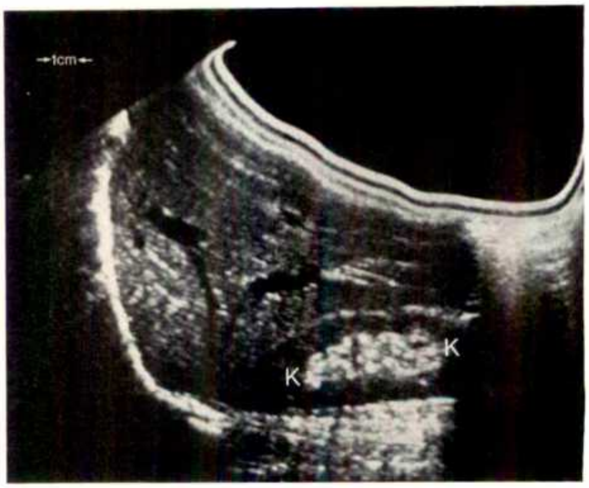

FIG. 13.
Longitudinal scan of the right upper abdomen, showing the right kidney (K) behind the liver (L)

very similar to chronic pancreatitis, though this is usually generalized, and the two diseases may coexist. Since the pancreatic tail is difficult to detect, lesions in this area may be missed unless they are fairly large—and therefore inoperable. Posterior scanning of the tail through the left kidney may help in some cases (Goldstein and Katragadda, 1978). Though the normal duct can sometimes be seen it is more easily detected when dilated and its value as a diagnostic sign in pancreatic disease has recently been reviewed (Gosink and Leopold, 1978). We have also occasionally found this sign to be of diagnostic value though it does not differentiate neoplastic from inflammatory causes of obstruction.

The jaundiced patient

Despite clinical findings and laboratory tests the exact cause of jaundice may be difficult to establish in many patients. Ultrasound has been shown to be nearly 100% correct in differentiating obstructive from hepatocellular jaundice since normal bile ducts cannot be seen, whilst dilated ducts are visible (Sample *et al.*, 1978). The level of obstruction can also be inferred by examination of the gall-bladder and common bile duct, though duodenal gas may prevent identification of the exact cause in about 30% of patients with lower common duct obstruction (Malini and Sabel, 1977). The dissolution of retained biliary calculi by ultrasound has also been reported recently but is still far from being an accepted clinical tool (Davies *et al.*, 1977).

GENITOURINARY SYSTEM

The female reproductive organs have been discussed under the section on gynaecology and this section will therefore include reference to the kidney, ureter, bladder, prostate, seminal vesicles and testes.

Kidney

The normal kidneys can be seen in virtually every patient. It has been customary to scan with the patient prone but the lower ribs often interfere with detection of the upper poles, especially the left. Anterior scans can be used to see the right kidney to advantage (see Fig. 13) in those patients whose liver is in contact with a high proportion of kidney (Taylor, 1976). Bowel gas prevents anterior scans being successful on the left.

The size, shape and position of the normal kidneys can be seen, though care must be taken to obtain length measurements during suspended respiration only (Skolnick *et al.*, 1975). Modern scanners permit display of the renal vessels (Filly and Goldberg, 1977) and small structures within the parenchyma. This ability is seldom of clinical value. The greatest value of ultrasound in renal diagnosis is for the further evaluation of mass lesions. Its accuracy for differentiating solid from cystic lesions is above 95% (Sherwood, 1975) and it can be used to assist with needle biopsy or aspiration (Goldberg and Pollack, 1973). Solid lesions are most likely to be primary carcinomata and the ultrasound characteristics of these are very variable. Almost all produce echoes above those of normal kidney but may have varying

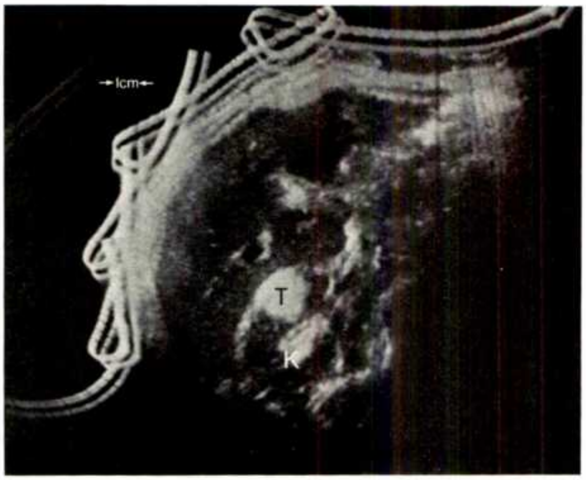

FIG. 14.

Transverse scan of right upper abdomen. A densely echogenic tumour (T) is present in the right kidney (K). This appearance is typical of benign hamartoma.

degrees of central haemorrhage or necrosis, which give rise to echo free zones (Green *et al.*, 1976). These may occupy a high proportion of the tumour or the tumour may be multicystic and thus cause diagnostic difficulty with ultrasound, as with other techniques. Detection of extension of the tumour into the vena cava has rarely been described (Greene, 1975). Benign tumours and hamartomatous lesions have also been described but cannot reliably be differentiated from malignant lesions on ultrasound criteria alone, although small, clearly defined and dense echogenic lesions are likely to be benign (Lee *et al.*, 1978) (Fig. 14).

Whilst the diagnosis of cyst may appear comparatively straightforward a number of important errors have been reported. Green *et al.* (1976) reported 15 false negatives in 312 cases. Errors included abscesses, haematoma, renal artery aneurysm, hydronephrosis and both homogeneous and cystic tumours.

Since ultrasound does not depend on renal function for detection of the kidney it is well suited to the investigation of non-visualized kidneys (Marangola *et al.*, 1976) most commonly finding hydronephrosis, pyonephrosis and renal agenesis as the cause of this entity. Similarly, renal failure may render urography inadequate, especially in the infant, and Boineau *et al.* (1975) found ultrasound most valuable in the investigation of infants with poor renal function.

Hydronephrosis can be diagnosed when there is early dilatation of the intra-renal collecting system (Barnett and Morley, 1972) and when more severe the diagnosis is generally more easily made though gross cases may simulate, and be indistinguishable from, cystic disease. Ultrasound is particularly useful in the evaluation of hydronephrosis in pregnancy. The accuracy of ultrasound diagnosis of early hydronephrosis has recently been investigated by Ellenbogen *et al.* (1978) with encouraging results. A similar ultrasound appearance may result from renal sinus lipomatosis though Yeh *et al.* (1977) are of the opinion that this condition produces a less clearly defined echo free zone within the kidney.

Perinephric fluid collections are also readily identified though it is not possible to differentiate urine, blood and pus. The transplanted kidney is particularly well suited to ultrasound examination as it lies just beneath the skin. Changes in its size can be detected and correlated with rejection episodes, hydronephrosis can be easily seen and perinephric collections of fluid diagnosed and monitored (Bartrum *et al.*, 1976).

Ureter

The normal ureters cannot be identified with current ultrasound equipment. However, like the bile ducts, they may become visible if dilated and ultrasound can be used both to detect and monitor the distention and to determine the level of the obstruction. Rarely a ureterocele may be identified and Nikapota and Wray (1978) have shown both hydroureter and ureterocele in one patient. Dilatation of the ureter is not the only sign of urinary tract obstruction and Ellenbogen *et al.* (1978) have recently reviewed their experiences. Using ultrasound to detect early dilatation of the renal pelvis they have a very high success rate for confirmation of obstruction, but at the expense of a 26% false positive diagnosis rate.

Bladder

Ever since the very early days of diagnostic ultrasound it has been appreciated that the distended urinary bladder can be easily seen (Donald, 1963). Whilst it is most commonly used as an ultrasound window to the pelvic contents, primary examination of the bladder is often quite valuable. Its size and shape can readily be assessed. Harrison *et al.* (1976) found ultrasound especially useful for the semi-quantitative assessment of residual urine volume in children.

Bladder papillomata are readily seen, though exclusion of small lesions depends upon meticulous technique. Carcinomata are also easily seen and invasion of the bladder wall can sometimes be inferred (Barnett and Morley, 1971; McLaughlin *et al.*, 1975) although accurate staging by ultrasound does not yet seem to have been achieved. The innocuous nature of ultrasound makes it especially valuable as a means of measuring progress or response to treatment, though the small, irritable post-radiotherapy bladder may be almost impossible to examine if it cannot be distended adequately.

The presence of calculi and diverticula can also be confirmed and ultrasound may complement radiography here.

Prostate and seminal vesicles

The prostate gland can be approached either through the distended urinary bladder or, using special apparatus, via the rectum. Its size has been assessed with considerable accuracy using abdominal scanning (Miller *et al.*, 1973) and its consistency and capsular integrity enabled Watanabe *et al.* (1975) to differentiate benign from malignant lesions with an accuracy of about 80%.

The seminal vesicles may be seen if enlarged due to cyst formation or inflammatory disease (Walls and Lin, 1975).

Testes

Ultrasound investigation of this readily palpable organ is seldom indicated but Pollock and Goldberg (1977b) have shown both the normal testes and a testicular tumour in the presence of a hydrocele.

Torsion of the testis can also be diagnosed and interruption of the vascular supply can be confirmed by Doppler studies (Pedersen *et al.*, 1975).

CARDIOLOGY

The field of cardiac ultrasound is almost a subspeciality in itself and it is not possible to cover all aspects of it within the space available here. Some excellent monographs on the subject are available (see suggested further reading list) and the reader who wishes to study echocardiography in depth is referred to these.

The clinical uses can conveniently be divided into functional studies and anatomical studies and the equipment used may be either a single transducer with time-position ("TP" or "M" mode) recording or, more recently, real-time scanners. ECG gating of a conventional "B" scanner has also been tried in an attempt to produce "stop action" images at various phases of the cardiac cycle (King, 1972). These images take a long time to assemble and have not yet found wide clinical acceptance.

Functional studies were initially confined to the mitral valve since this was the easiest structure to locate (Edler, 1961) but the feasibility of obtaining meaningful records from the other cardiac valves was appreciated even at that time. Modern cardiac ultrasound is still most commonly aimed at recording the excursions of the anterior cusp of the mitral valve. From these records it is now possible to measure the amplitude and velocity of movement, to detect valve thickening and vegetations and to note fluttering caused by aortic incompetence (Ross, 1977). Somewhat similar records can be obtained from the tricuspid valve in a fair proportion of patients though they are rather less valuable clinically, mostly because left-sided disease is more common than right.

Studies of mitral valve dynamics permit the diagnosis of incompetence whilst stenosis can be both diagnosed and its severity judged (Gustafson, 1967). Abnormal valve mobility and prolapse due to rupture of the chordae can also be diagnosed, though a TP scan appearance once thought to be due to prolapse has recently been disproved by real-time scanning.

The movements of the aortic valve cusps can also be recorded and may permit the diagnosis and grading of aortic stenosis (Gramiak and Shah, 1970). The pulmonary valve is the most difficult to identify, but fortunately is less commonly the site of disease than are the other valves.

The AP dimensions of the left atrium and ventricle can be measured throughout the cardiac cycle and more sophisticated measurements permit the calculation of left ventricular volume, ejection fraction and cardiac output with an acceptable accuracy (Pombo *et al.*, 1971). The muscle wall thickness and muscle fibre shortening velocity can also be calculated and may yield valuable information about cardiac function, especially in the cardiomyopathies (Paraskos *et al.*, 1971).

Anatomical studies are generally aimed at the diagnosis or exclusion of pericardial effusion (Pridie and Turnbull, 1968) and left atrial myxoma (Petsas *et al.*, 1976) though a characteristic pattern may also be seen in HOCM and Godman *et al.* (1974) found it very valuable in the diagnosis of congenital heart disease in neonates. Use of the strip chart recorder to print out a continuous record of the echocardiographic information during an arc scan of the transducer over the chest permits the continuity of aortic root and mitral valve to be confirmed and may permit septal defects to be detected. However, there seems little doubt that the advent of real time scanners will permit the diagnosis of anatomical lesions to be made with greater speed and accuracy (Maron *et al.*, 1975).

VASCULAR IMAGING

The abdominal aorta is readily imaged in most patients, failures being due to overlying bowel gas. The dimensions of the vessel are easily measured (Fig. 15) and ectasia or aneurysm confirmed or excluded (Leopold, 1970). Grey scale display also permits simultaneous display of any thrombus within the aneurysm (Meire, 1978). The thoracic aorta is usually impossible to image as it is obscured by lung and bone. However, when it is sufficiently dilated to reach the chest wall it may be possible to measure its dimensions and Goldberg and Lehman (1970) found it possible to detect thoracic dissections in some patients.

The inferior vena cava is also readily seen and its changes in diameter with respiration and the cardiac cycle can be monitored. Weill and Maurat (1974) noted dilatation of the IVC in right sided heart failure whilst Walls and Templeton (1977) observed indentation of the cava in patients with tumours of the pancreatic head. Many other workers, including the author, have not found these signs specific.

More recently there has been considerable interest in visualization of the major branches of the aorta, particularly in the upper abdomen when they may be used as landmarks for locating the pancreas (Leopold, 1975). The coeliac axis, hepatic, splenic, superior mensenteric and renal arteries are frequently seen (Filly and Carlsen, 1976) though I am unaware of any example of identification of the renal arteries in a patient with aortic aneurysm, which is probably the only situation when their identification might be clinically useful.

Many veins may also be shown but the components of the portal system are the most valuable as they may be distended in portal hypertension and can also be used as anatomical reference points.

Doppler ultrasound can be used to indicate flow velocity within vessels though it is doubtful whether this is really within the sphere of interest of radiologists as it is not an imaging procedure. Gosling has made a special study of this procedure and has recently reviewed his technique (Gosling, 1978). Using continuous wave ultrasound and on line frequency spectrum analysis he is able to assess the functional state of a vessel and draw certain conclusions about the type and severity of disease and the efficacy of the collateral vessels. His group have also constructed a scanner which permits vessel imaging and has proved clinically useful (Lewis *et al.*, 1978). A similar device with colour coding of the velocity signal has been evaluated by White and Curry (1978) and has seen extensive clinical use in Canada.

A more complex pulsed Doppler device has been constructed by Fish (1975) (Fig. 16) and permits flow profile to be measured. Further development of such a system will permit calculation of volume flow in accessible vessels.

NEUROLOGY

Many years have passed since the first description of ultrasonic detection of the cerebral mid-line echo. More than any other examination echoencephalography has produced two schools of opinion, the protagonists and the antagonists. The main reason

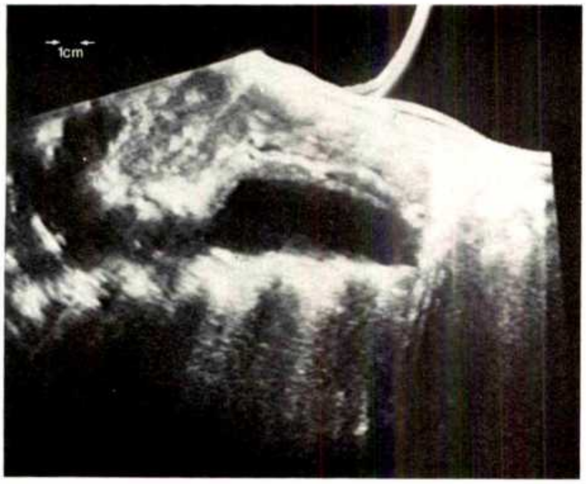

FIG. 15.
Longitudinal scan of abdominal aorta demonstrating a fusiform aneurysm.

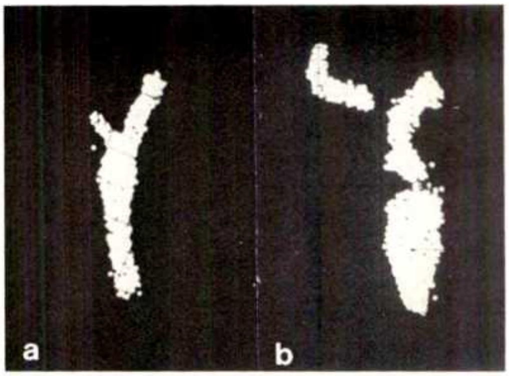

FIG. 16.

(a) Pulsed Doppler ultrasound image of a normal carotid bifurcation.

(b) An abnormal vessel containing an area of ectasia and two very severe stenoses (by courtesy of Mr. C. Wood, Ultrasound Department, Clinical Research Centre).

for this is the high degree of operator dependance of this technique. Kazner worked in a busy neurology centre and has taken a great personal interest in the technique. Each examination was performed in a full knowledge of the patient's clinical conditions and, as might be expected, his results were exceptionally good (Schiefer and Kazner, 1966). Conversely, in many hospitals the examination is delegated to a junior member of staff with little knowledge or experience of the subject and, in this situation, the results are meaningless or frankly misleading. The advent of computed tomography has so revolutionized cerebral diagnosis that ultrasound is likely to be used less and less. This is especially so since the high, posterior, inferior or bilateral lesions which do not cause shift of the mid-line can all readily be seen with computed tomography.

Automatic "mid-line computers" have been introduced in order to attempt to reduce the operator dependance of echoencephalography but have proved only marginally more satisfactory.

A more promising development in the field of neurological ultrasound is the investigation of the cerebral circulation with the pulsed Doppler systems discussed in the previous section. These have the capability of detecting stenosis in the extra cranial arteries and can quantify the severity and haemodynamic significance of the lesion.

Cerebral B scanning is generally unsuccessful owing to distortion and reflection of the ultrasound beam by the skull. In the neonate and infant, however, the thinner and more uniform cranium does permit excellent images to be obtained and Garrett and Kossoff (1977) have found these most useful in the management of conditions affecting ventricular size.

OPHTHALMOLOGY

Ultrasound has been used for over two decades for the measurement of eye length whilst ophthalmic "B" scanning was first reported twenty years ago (Baum and Greenwood, 1958). The images obtained by Baum have seldom been bettered to this day and, as with other special procedures, the best results have been obtained by those who devote most of their time to the technique.

One of the major roles of ultrasound in ophthalmology is in the investigation of the opaque eye (Coleman, 1972). Cataracts transmit ultrasound and thus vitreous abnormality and retinal detachment can be excluded before surgery is contemplated. The severity of vitreous haemorrhage or retinal detachment can be gauged, underlying pathology sought and their progress monitored. Intra-ocular and orbital tumours are readily seen and, using careful analysis of the "A" scan from a tumour, Ossoinig (1974) has achieved very high accuracy in the differential diagnosis of ocular masses.

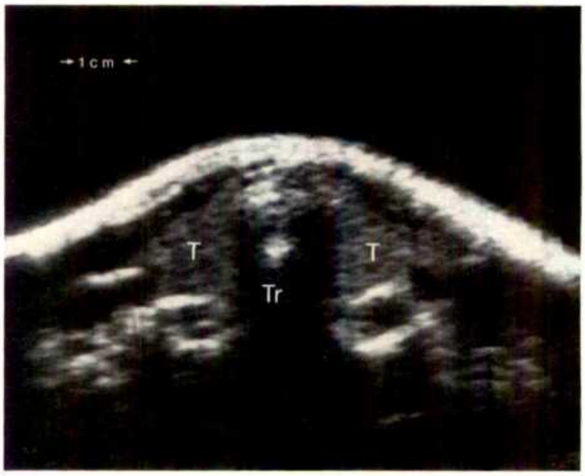

FIG. 17.

Transverse scan of a normal thyroid gland (T). Trachea (Tr).

Almost all the orbital contents can be seen and abnormalities of the cornea, lens, anterior chamber, optic nerve and oculomotor muscles have also been reported (Francois and Goes, 1976).

ENDOCRINOLOGY

This is a convenient heading under which to group examination of the thyroid, parathyroid and adrenal glands.

The normal thyroid gland can be clearly seen by ultrasound in every patient, but is optimally demonstrated if a water bath is used in conjunction with grey scale display and a transducer of about 5 MHz (Fig. 17). In general, ultrasound investigation is used to evaluate mass lesions whether detected clinically or on isotope scan. Differentiation of solid from cystic masses is easily achieved and recent work has been aimed at identifying the echo patterns of specific diseases. "A" scan analysis may be helpful (Ramsey and Meire, 1975) and a very heterogeneous pattern results from multinodular goitre (Fig.18). Conversely, acute inflammatory disease, lymphocytic thyroiditis and most malignant tumours return echoes of reduced intensity and these diseases cannot be differentiated on the basis of echo pattern alone.

The normal parathyroid glands are not detectable by current commercially available equipment but higher frequency scanners with improved resolution

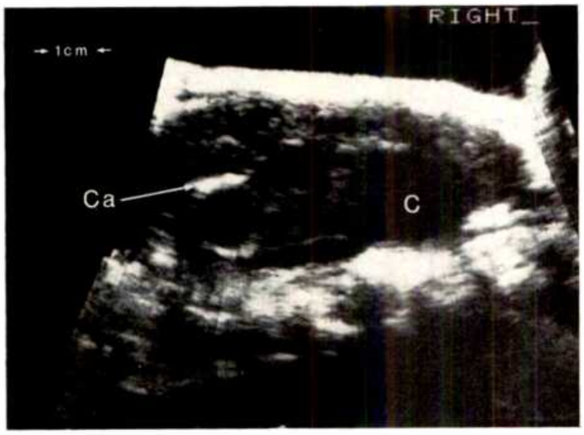

FIG. 18.

Longitudinal scan of a right lobe of thyroid, demonstrating both cystic areas (C) and calcification (Ca) in a multinodular goitre.

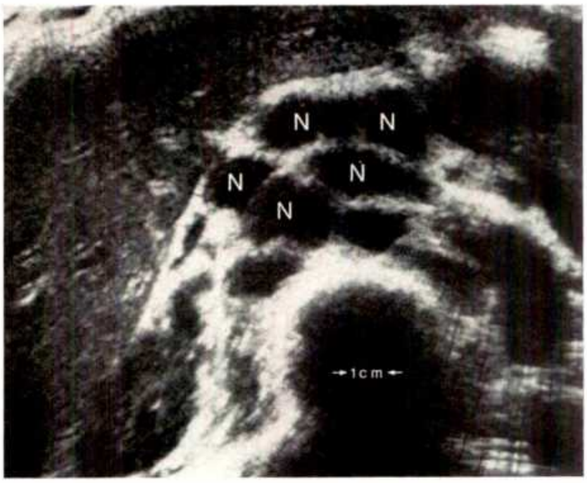

FIG. 19.

Transverse scan of the upper abdomen showing multiple enlarged para-aortic lymph nodes (N).

and better grey scale display may well permit parathyroid visualization. To date only relatively large tumours have been detected by ultrasound (Crocker *et al.*, 1978).

The normal adrenal glands are also very difficult to identify in most patients though Sample (1978) has devized a scanning approach which should help. Adrenal masses greater than 3 cm are more easily detected (Bernadino *et al.*, 1978) and should be sought in patients with biochemical evidence of adrenal tumour. It must be remembered though that many endocrinologically active lesions are microscopic in size!

RETICULO-ENDOTHELIAL SYSTEM AND RETROPERITONEUM

The spleen is one of the more difficult organs to assess clinically and it has to reach three to four times its normal volume before it is readily palpable. Ultrasound can image the normal spleen and can be used to gauge splenic size. Rasmussen *et al.* (1973) have described a technique for measuring splenic volume but it is rather tedious and not very accurate on small spleens. Koga and Morikawa (1975) prefer measurement of splenic area as seen on a section in the eighth intercostal space whilst Taylor (1978) favours measurement of the maximum length of spleen seen on a section in the tenth interspace. Taylor's technique is certainly easiest and he suggests that measurements over about 11 cm indicate enlargement.

Taylor has also described a range of echo patterns in cases of chronic splenomegaly which apparently correlate well with the disease process involved (Taylor and Milan, 1976). In general, inflammatory diseases produce high intensity echoes and untreated neoplastic disorders may result in a homogeneous low amplitude pattern.

However, the echo pattern in neoplastic spleens undergoing chemotherapy or radiotherapy may well alter and produce a more echogenic appearance. It is therefore essential for the ultrasonographer to be fully conversant with the patient's clinical details before meaningful interpretation of the ultrasound findings can be achieved. It is possible that changes in the ultrasound characteristics of treated tumours may be a useful index of the response to therapy.

Lymphadenopathy can be detected only when the nodes or node masses reach at least two or three centimetres diameter. The para aortic and mesenteric nodes are the most readily seen, though bowel gas may limit success in about one fifth of all patients. Ultrasound is therefore a useful staging procedure for patients with lymphoma and other malignancies which may involve these nodes (Tyrrell *et al.*, 1977; Filly *et al.*, 1976) (Fig. 19). A negative scan does not exclude involvement.

Lymphoma tissue at almost any site appears very homogeneous to ultrasound resulting in an almost echo free appearance and this characteristic may permit a correct diagnosis of the nature of the mass at an unusual site.

Within the retroperitoneal space a number of mass lesions may arise and prove difficult to locate and identify. Ultrasound has proved useful in this area and the detection of sarcomas, liposarcomas, cystic hygromas, urinomas and ideopathic fibrosis have all been described (Pollack and Goldberg, 1977a; Sanders *et al.*, 1977; McCullough and Leopold, 1976).

ONCOLOGY

Ultrasound scanning is valuable at four different stages in oncology, initial diagnosis, staging, radiation therapy planning and tumour follow-up.

Whilst initial diagnosis may be made with tumours at many different sites renal and pancreatic primaries are more likely to be seen initially by ultrasound. The staging of tumours depends on detection of local and distant spread and both these can be demonstrated. The planning of radiation therapy requires an accurate knowledge of tumour size and shape and the relationship of normal organs to the proposed treatment fields. Ultrasound will supply much of this information and has been shown to aid treatment planning (Brascho, 1974; 1978). The availability of digital memories in place of the current scan converters will facilitate the interfacing of ultrasonic scanners with treatment planning computers.

The speed and ease of ultrasound scanning also makes it an ideal system for following the progress of a lesion and assessing the response to treatment (Fig. 20). Therapy fields can be tailored to reduce the dose to adjacent normal tissues as a tumour regresses.

RESPIRATORY SYSTEM AND THORAX

The almost complete reflection of ultrasound at gas interfaces severely limits the value of this technique in the respiratory system. However, a number of enterprising workers have attempted its use and have achieved clinically valid results. The demonstration of fluid collections in the maxillary antrum (Brzezinska, 1972) pleural effusions in the chest (Landay and Harless, 1977) and intra-thoracic masses (Hirsch *et al.*, 1978) has been shown to be possible, though none of these can be regarded as routine uses of the technique. In our experience pleural effusion is most often diagnosed incidentally when examining the liver. Ultrasound may also be of value in the treatment of pleural effusions since the optimal site for placement of the aspiration needle can easily be identified.

BREAST

The hope that ultrasound could be used for the diagnosis of early breast cancer has not yet been fulfilled. Many researchers have devoted their energies to this end in the USA (Baum, 1977), Japan (Wagai *et al.*, 1976) and Australia (Jellins *et al.*, 1975) but none has met with profound success. The Japanese, though, do seem to have achieved favourable results, probably due either to greater diligence or, more likely, the small size of the average Japanese breast. The larger Western breasts with greater proportions of fibrous and adipose tissues are far from ideal organs from an ultrasonic viewpoint! The recent report of increased Doppler frequencies from the vessels around neoplasms may prove to be an additional sign worthy of pursuit (Wells *et al.*, 1977).

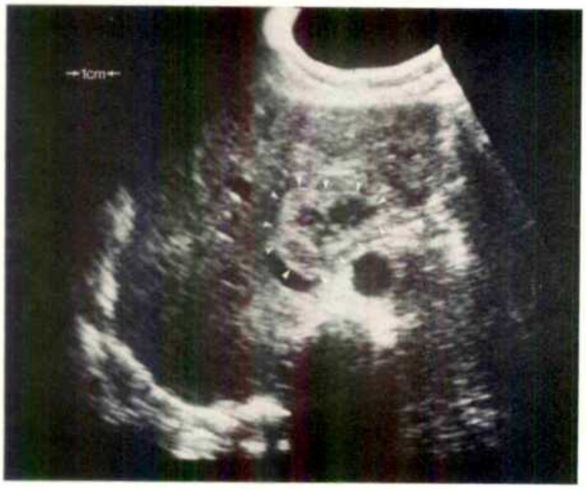

FIG. 20A.

Transverse scan of a liver. The caudate lobe (arrowed) is enlarged by a partially necrotic echogenic metastasis.

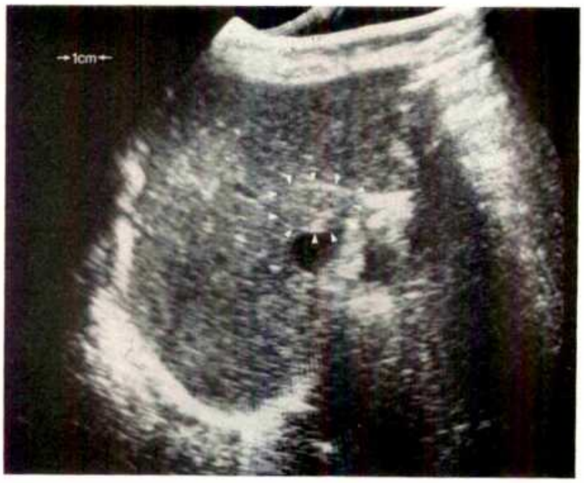

FIG. 20B.

Same patient as (A) after three months of chemotherapy. The caudate lobe (arrowed) is now normal in size.

ORTHOPAEDICS AND RHEUMATOLOGY

As with the lungs the almost total reflection of ultrasound by bones has limited the value of this form of diagnosis in orthopaedics. Despite this it has been shown that the progress of a healing long bone fracture can be monitored by ultrasound (Brown and Mayor, 1976) and the soft tissue extents of primary bony tumours is better outlined than by most other forms of imaging (Kratochwil and Zweymuller, 1975).

Whilst joints are not accessible to ultrasonic examination the soft tissues around them can be displayed and useful information can be obtained concerning Baker's cysts (Meire *et al.*, 1974) and synovial thickening (Fig. 21).

Ultrasound has also been shown to be very valuable as a method of treating soft tissue conditions but this work is beyond the scope of this paper.

REAL-TIME SCANNERS

These devices produce rapid sequential images of the area under examination. They are automatic and permit the observer to view moving structures "in real-time". Their major advantages are their ease of use and freedom of movement of the scanning head. At the present time, the still images obtained are not comparable with those from a conventional machine in terms of resolution or grey scale quality, but rapid progress is being made.

Whilst they would be expected to be helpful in cardiac diagnosis, especially in the investigation of congenital anatomical anomalies, they are also very valuable for rapid survey scanning. A normal early pregnancy can be assessed in a few seconds, an adequate BPD measurement obtained, major abnormalities excluded and an adequate placental localization achieved in many cases. Their value in the diagnosis of spina bifida and other less gross lesions remains to be proven but will undoubtedly increase as technical performance improves.

Outside the field of obstetrics they are useful for the rapid examination of organs such as the kidneys and aorta and will probably prove useful in pancreatic and liver imaging. We have found real-time especially useful for identifying vascular structures around the porta hepatis since the scanner can be moved into any plane and the vascular connections rapidly ascertained.

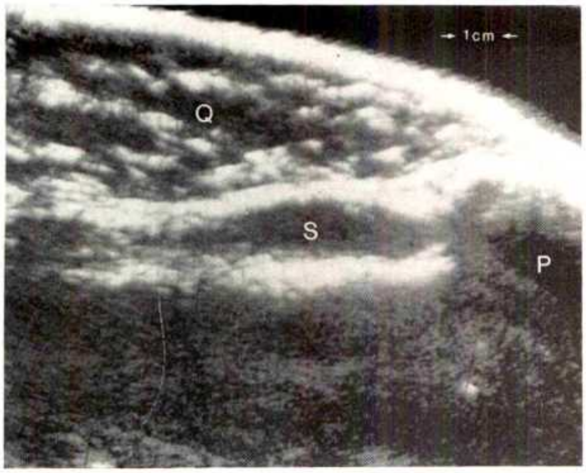

FIG. 21.

Anterior longitudinal scan of a knee in a patient with rheumatoid arthritis. There is synovial thickening in the supra patellar pouch (S). Patella (P) quadriceps muscles (Q).

ASPIRATION/BIOPSY

Modern medical practice has come to accept the percutaneous passage of fine needles into many parts of the anatomy in order to obtain fluid or cells for diagnosis. Correct diagnosis depends on correct placement of the needle tip and ultrasound can help with this. Several different systems have been described but, in general, the area of interest is identified on a "B" scan and then the needle guided alongside or through the transducer. This technique has been used for renal cyst puncture (Goldberg and Pollack, 1973) pancreatic cytology (Hancke *et al.*, 1975) and many other procedures including amniocentesis, pericardiocentesis, renal and liver biopsy (Holm and Gammelgaard, 1978; Goldberg, 1978).

COMPARISON WITH OTHER TECHNIQUES

It is possible that this is the most important section of this paper since the ever widening range of diagnostic techniques available cannot and should not all be used on every diagnostic problem.

In so far as ultrasound can be regarded as competing with other procedures its main rivals are conventional radiography (including contrast studies), computed X-ray tomography (CT) and radionuclide scanning. Ultrasound does not rely on organ function in order to produce an image but, by the same token, gives little or no direct information about function. Conversely, the modern radiopharmaceuticals permit quite sophisticated functional studies and each technique may now complement the other. As an imaging procedure ultrasound competes most directly with X-radiological techniques. Since there is a known small, potential hazard from X-radiations it is probably correct, where appropriate, to perform the relevant ultrasound study first and then only to procede to radiology after a failed examination or where further information is required. This is clearly the case when looking for a lost IUCD and is almost certainly so for the liver, the jaundiced patient, abdominal aorta and, where expertise exists, the pancreas (Husband *et al.*, 1977; Kreel and Meire, 1977; Meire and Kreel, 1978).

In obstetrics and cardiology the information obtained may not be available via any other technique. In common with other "special procedures" a considerable amount of operator expertise is essential and it is clearly desirable for the operator to have a full knowledge of the anatomy and pathology of the area being studied. Where operator expertise is not available an ultrasound machine is useless. A CT scanner, however, requires less manipulation by the user in order to obtain a first class image, though the same medical knowledge is required by the interpreter. The high degree of operator dependance is a severe limitation of current ultrasound equipment, but continuing technical developments will doubtless reduce the duties of the ultrasonographer.

FURTHER READING LIST

Books on principles and technique of ultrasonography

Diagnostic Ultrasonics. By W. N. McDicken (Crosby, Lockwood, Staples, London).

A User's Guide to Diagnostic Ultrasound. By Shirley, Blackwell, Cusick, Farman and Vicary (Pitman Medical Publishing Company, Tunbridge Wells, England).

Practical Abdominal Ultrasound. By Constantine Metreweli (William Heinemann Medical Books Ltd., London).

Biomedical Ultrasonics. By P. N. T. Wells (Academic Press, London).

Recent Advances in Ultrasound in Biomedicine. Vol. 1. Editor D. N. White (Research Studies Press, USA).

Books on clinical applications

Ultrasonics in Clinical Diagnosis. By P. N. T. Wells (Churchill Livingston, London).

Atlas of Gray Scale Ultrasonography. By K. J. W. Taylor (Churchill Livingston, New York).

Diagnostic Ultrasound in Gastrointestinal Disease. By K. J. W. Taylor (Churchill Livingston, New York).

Abdominal Gray Sale Ultrasonography. By B. B. Goldberg (John Wiley & Sons, New York).

Ultrasonography in Obstetrics and Gynaecology. By R. C. Saunders and A. E. James (Appleton Century Crofts, New York).

Textbook of Diagnostic Ultrasonography. By S. L. Hagen-Ansert (C. V. Mosby Company, Saint Louis, USA).

Echocariography. By H. Feigenbaum (Lea & Febiger, Philadelphia, USA).

Cardiac Ultrasound. By R. Gramiak and R. C. Wagg. (The C. V. Mosby Company, Saint Louis, USA).

Handbook of Clinical Ultrasound. By M. de Vlieger *et al.* (John Wiley & Sons, New York).

Ultrasound in Tumour Diagnosis. By C. R. Hill *et al.* (Pitman Medical, London).

Medical Imaging. By L. Kreel (H. M. & M., Aylesbury, England).

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Book review

Urology in Practice. Edited by Charles J. Devine, Jr. and John F. Stecker, Jr. pp. xxii+998, 1978 (Little, Brown & Co., Boston). $48.50.
ISBN 0-316-18155-2

This is a large, 1000 page book with 68 chapters written by 81 authors. It is in twelve parts, beginning with anatomy, physiology and embryology. Part II is "Evaluation of the Urologic Patient", including radionuclide and ultrasound as well as X-ray techniques. Other parts cover a great variety of adult and children's disorders, their management and surgery. "Why another one?" the editors ask in their preface; "what do we have to offer that is not available in the current texts?" They point to a gap they wish to fill, a book addressed to the senior resident in urology. They selected authors who were "strong in theory, but also experienced in practice, to write on the various aspects of urology in which they have a primary interest".

The range of the book is wide. There are not just the expected chapter headings, like "Tumors of the kidney", but also in the same section "Current concepts in immunobiology of genitourinary tumors". The writing is densely packed, two columns to a page, often in long descriptive chunks with few breaks. Chapter 12 on radionuclide scanning for instance, does not have one illustration. This is therefore a book for the urology registrar to take on study leave, or to bed, but not for reference or revision under pressure of time. I longed for the odd table or diagram to save me from becoming bogged down, and would argue that teaching is more effective if it is made less stolid. The one contributor from this country, J. H. Johnston, points the way with his elegantly varied chapter on "Anomalies of the bladder; epispadias". Other notable exceptions to the prevailing style are Keith Waterhouse on "Lower urinary tract obstruction in children" (splendid flow diagram on management), and R. F. Gittes on "The adrenals" (excellent diagrams and illustrations, except for one washed-out X-ray reproduction, Fig. 41–4A).

The interested radiologist will ask "is this a book for me?" The X-ray illustrations, it must be said, are not always of the first quality. The conscientious reviewer will also point to muddles like Fig. 14–14 which reappears almost at once as Fig. 14–20 (but this time with the correct legend), and Fig. 29–4 (upside down). Quibbles aside, the book is replete with expert knowledge. No doubt radiologists will occasionally like to consult it when a point of urological detail comes up for debate. But the volume is primarily addressed to the urologist in training and in practice, so that its place should be in the hospital's not the X-ray department's library.

THOMAS SHERWOOD.

1979, *British Journal of Radiology*, 52, 704–708

Bilateral extracranial internal carotid artery injury due to non-penetrating trauma—report of three cases

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Abstract

Angiographic features of three patients with bilateral internal carotid artery injury (spasm/dissection/thrombosis) due to non-penetrating trauma are reported. All three patients were involved in motor vehicle accidents. Focal-localizing neurological signs were present and the patients were suspected of having extracerebral haematomas. The diagnosis of traumatic spasm/dissection/thrombosis of the cervical portion of the internal carotid arteries was made following angiography. The need to include views of the cervical carotid arteries in cases of traumatic hemiparesis is stressed and possible effect of cranial CT scanning in these patients on diagnosis of carotid artery injury discussed.

Spasm and thrombosis (with or without complete occlusion) of the extracranial internal carotid artery resulting from blunt trauma has been reported not infrequently in medical literature. However, to date there has only been one report of bilateral internal carotid thrombosis associated with non-penetrating trauma (Ojemann and Moser, 1964). All three patients described here with bilateral carotid artery injury were suspected of having an epi- or subdural haematoma and the diagnosis was not made until carotid angiography was carried out.

Case Reports

Case 1

A forty-four-year-old woman, who was the driver of a car involved in a head-on collision, was admitted to another hospital complaining of left hip pain. She was wearing a seat belt and was not displaced from her seat. There was no evidence of trauma to the head and neck. Radiographs of the pelvis and left hip did not reveal any fracture. Two-and-a-half hours following admission she had a grand-mal fit and was transferred to Royal Perth Hospital where a neurological examination revealed a left hemiparesis. Again, no external evidence of head and neck injury was detected. Skull and cervical spine radiographs showed no abnormality. Clinical diagnosis of acute right subdural haematoma was made and a bilateral carotid angiogram was carried out. This showed severe, remarkably symmetrical, luminal narrowing and irregularity of both the internal carotid arteries (Figs. 1 and 2). Angiographic interpretation was that the patient had suffered a non-penetrating injury to the cervical portion of the two internal carotid arteries resulting in intimal tears associated with severe spasm and thrombosis. There was no intracranial space occupying lesion and left hemiparesis was thought to be due to distal embolization. The patient was anti-coagulated and despite extensive rehabilitation, has made no neurological recovery.

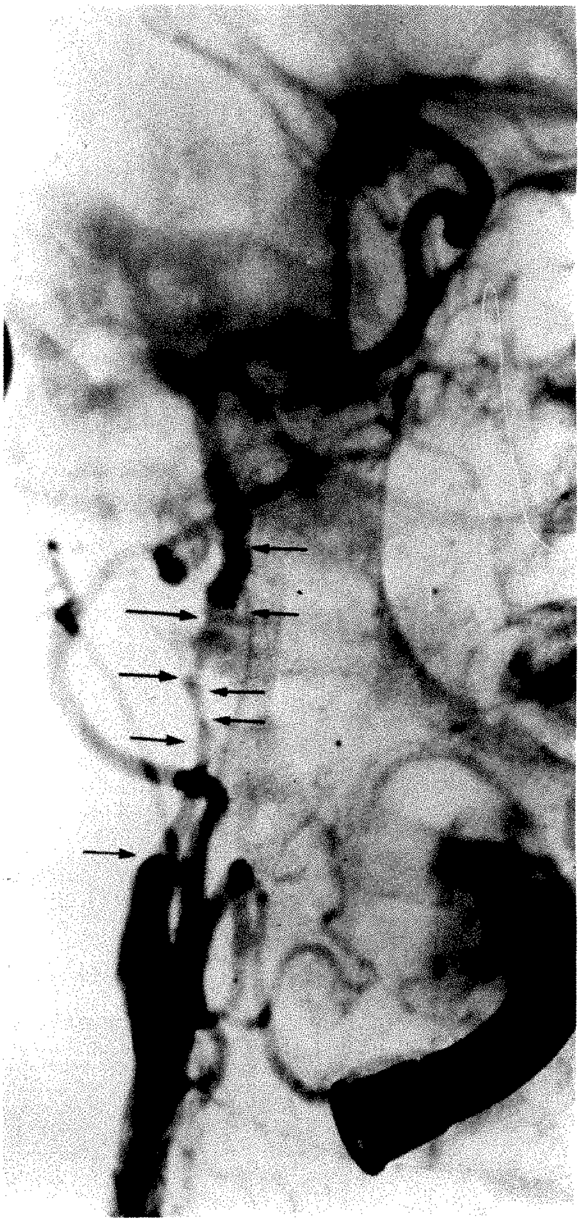

Fig. 1.

Right carotid angiogram.

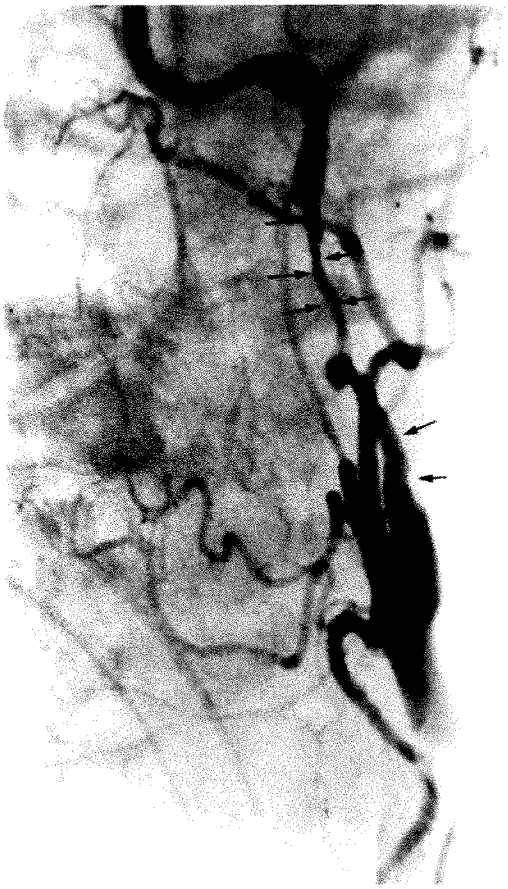

FIG. 2.

Left carotid angiogram. Oblique views showing, as on the right, severe luminal irregularity and narrowing of the internal carotid artery.

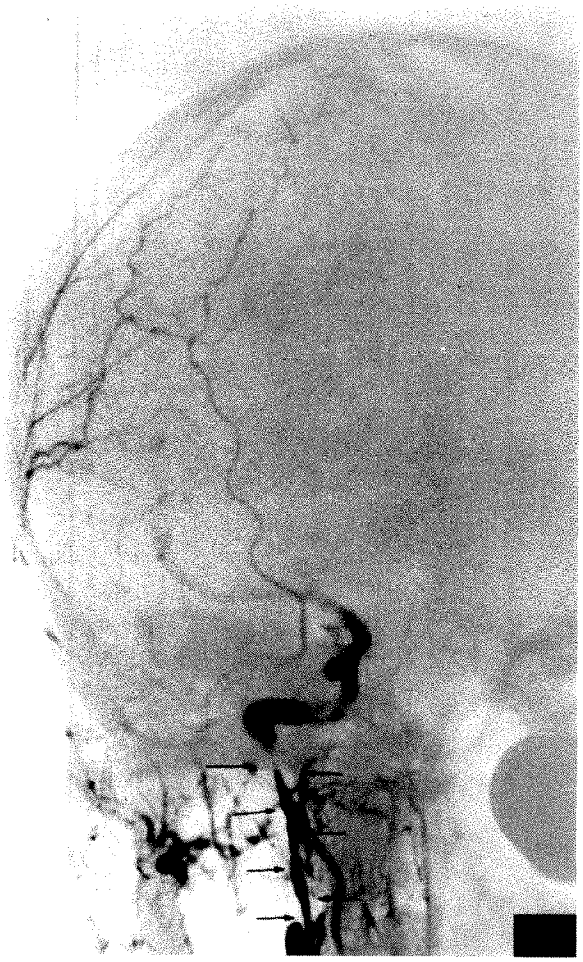

FIG. 3.

Right carotid angiogram showing intimal dissection and narrowing of the lumen of internal carotid artery.

Case 2

A twenty-two-year-old girl (front seat passenger) was thrown out of the car which was involved in an accident. When seen in casualty, she was stuporose and had a left hemiparesis. There was no evidence of trauma to the neck. Radiographs revealed a linear fracture of the right parietal bone. Cervical spine radiographs showed no abnormality. A clinical diagnosis of right-sided epidural haematoma was made. Angiography revealed intimal dissection with incomplete thrombosis of the right internal carotid artery extending from 2.5 cm beyond the bifurcation to the base of the skull, with poor perfusion of the middle cerebral artery (Fig. 3). The left internal carotid artery showed extensive smooth narrowing due to traumatic spasm (Fig. 4). Both the anterior cerebral arteries opacified from the left side. The patient was treated with Dexamethasone and Rheomacrodex. Follow-up 18 months later shows good neurological recovery with minimal residual weakness of the left leg.

Case 3

A twenty-year-old girl was the front seat passenger in a car which was involved in a head-on collision. She was wearing a seat belt and was restrained in her seat. On admission, she was noted to have a right hemiplegia. There was no evidence of injury to the neck and the admitting casualty officer remarked that the carotid artery pulsations were present and normal. Skull and cervical spine radiographs were normal. Clinically she was suspected of having an acute left-sided subdural haematoma. Angiography revealed complete occlusion of the left internal carotid artery, secondary to traumatic thrombosis extending from 3.0 cm above the bifurcation up to the intracavernous portion of the carotid artery (Fig. 5). The right internal carotid artery showed spasm of a 3.5 cm length of the carotid artery just below the base of the skull (Fig. 6). There was no intracranial space effect. At operation, the presence of traumatic intimal dissection and thrombosis of the left internal carotid artery was confirmed and an endarterectomy was carried out. The adventitia was noted to be intact. Post-operatively she deteriorated and died. Post-mortem examination revealed re-thrombosis of the left internal carotid artery. The right carotid artery was intact and of normal calibre along its entire length, confirming that the segmental narrowing seen on angiography was due to spasm without underlying intimal damage.

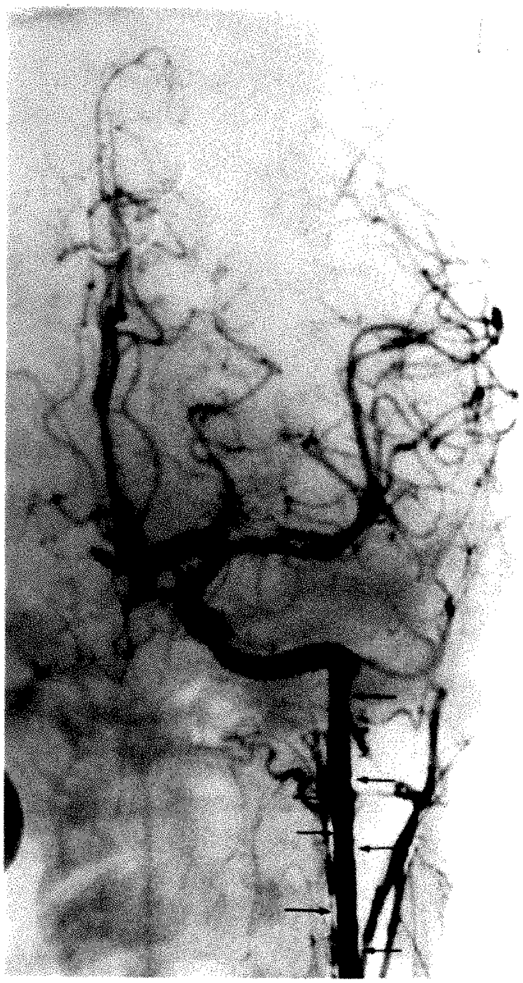

Fig. 4.

Left carotid angiogram showing extensive spasm and "straightening" of the internal carotid artery.

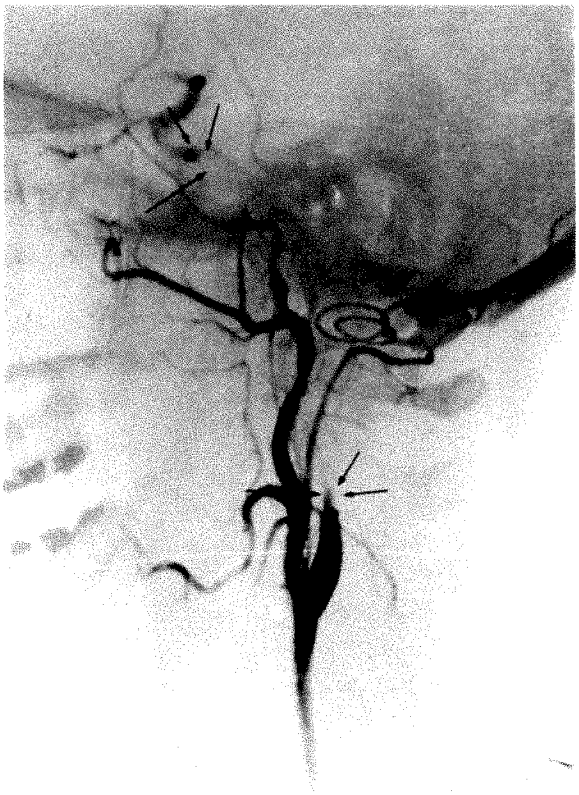

Fig. 5.

Left carotid angiogram showing complete traumatic thrombosis of the internal carotid artery from 3.0 cm above the bifurcation. Note the retrograde filling of the terminal carotid artery.

Discussion

In the last three years, we have documented seven cases of internal carotid artery injury following non-penetrating trauma to the neck. Of these, the three cases presented here showed bilateral carotid artery lesions. It is accepted that contusion or stretching of a major artery can damage the intima and media of that vessel (Gurdjian *et al.*, 1971), to cause its occlusion by spasm or thrombosis (Houck *et al.*, 1964). Intimal lacerations may lead to stripping of the intima where the dissected lining forms a plug and occludes the vessel or the intimal tear becomes the site of thrombus formation. Injury to the intima and media may also lead to aneurysm formation (Sullivan *et al.*, 1973). It is of interest to note that in two of the cases reported here (Nos. 2 and 3) the site of the arterial spasm corresponds to the anatomical explanation put forward by New and Momose (1969). They noted that the distal portion of the cervical carotid artery lies anterior to the lateral articular mass of the atlas. Extension of the head and neck stretches and partly fixes the carotid artery at this level, and contralateral rotation of the head occurring at the atlanto-axial joint further stretches the artery. These two movements carried out suddenly and to the extreme are likely to cause focal compression of the internal carotid artery.

None of the three cases reported here was suspected of having carotid artery injury. Yamada, in a study of 52 cases of injury to the internal carotid artery due to acute non-penetrating trauma, found that only three of the 52 cases were admitted with the diagnosis of carotid artery insufficiency

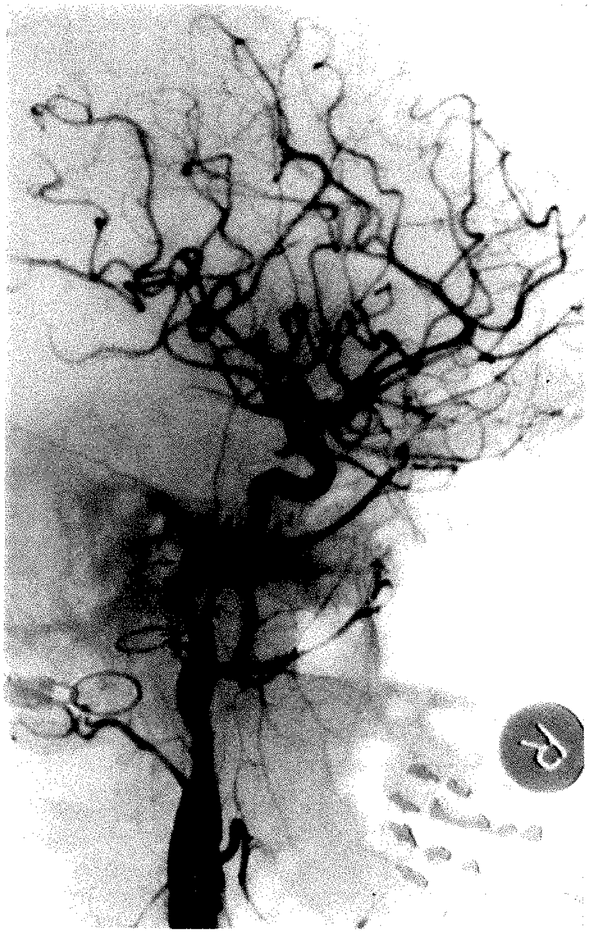

FIG. 6.
Right carotid angiogram showing spasm of the internal carotid artery below the skull base.

due to trauma (Yamada *et al.*, 1967). Diagnosis of carotid artery occlusions in non-penetrating injuries is very difficult as the clinical picture resembles that of the more common epi- or subdural haematoma. That the pulsation of vessels in the neck is of poor diagnostic value has been amply confirmed by our third case (Schneider and Lammens 1952). It has been said in the past and this article concurs, that apart from an autopsy, angiography is the only accurate method of diagnosing traumatic lesions of the carotid artery (Gurdjian *et al.*, 1963). Development of neurological signs may be delayed up to 24 hours. The latent period probably represents the time necessary for the formation of thrombus and subsequent occlusion of the vessel or distal embolization. Case 1 reported in this paper had no neurological symptoms or signs when first seen; left hemiparesis was noted following a grand-mal seizure two-and-a-half hours after admission.

Cranial CT scanning, rightly, is now the first investigation in patients involved in motor vehicle accidents who are suspected of having intra- or extra-cerebral haematoma. However, one should be aware that the patients with a negative cranial CT scan, who have definite neurological signs, may have carotid artery injury even though there may not be any external manifestation of trauma to the neck. Already CT scanning has led to a great reduction in angiograms carried out in most neurosurgical centres. This decrease in the number of carotid angiograms in patients with suspected head trauma may, in fact, lead to a "false" reduction in the number of diagnosed carotid artery injuries from non-penetrating trauma. When carotid angiography is carried out in patients suspected of having epi- or subdural haematoma, it is imperative that the views of the cervical portion of the carotid arteries are included. If this is not done, then patients who are suffering from spasm/dissection/thrombosis of the extracranial portion of the internal carotid artery will be missed (Zilkha, 1970). Also, as indicated in this report, it is not unusual to see bilateral lesions. It is the policy of the Department of Diagnostic Radiology to carry out bilateral carotid angiography in all trauma cases suspected of having epi- or subdural haematoma. We feel that the high detection rate (three out of seven) of bilateral carotid artery lesions in our experience is the result of this policy. At Royal Perth Hospital, most of the cerebral angiography is performed by transfemoral catheterization. This approach, we feel, minimizes the risks of iatrogenic damage to the carotid arteries and allows bilateral carotid angiography to be carried out without much difficulty. In all three of our cases, post-traumatic hemiplegia was the reason for angiography. If the angiographic study had been limited to the appropriate side, bilaterality of lesions would not have been recognized. We would like to suggest that bilateral internal carotid artery injury is not uncommon in patients with non-penetrating trauma to the neck. A limited angiographic study advocated in the past (Murray, 1957) would account for the lack of previous reports indicating the bilaterality of lesions.

ACKNOWLEDGMENTS

I thank all members of the Department of Diagnostic Radiology for their encouragement and also thank the staff of the Department of Neurosurgery for allowing me to study these patients. My thanks also to Miss Alison Swales for typing this manuscript.

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Book review

Corcadeus' Gynaecologic Cancer (Fith Edition). Edited by S. B. Gusberg and H. C. Frick II, pp. xii+494, 1978 (The Williams and Wilkins Company, Baltimore), $49.50. ISBN 0-683-03854-0.

In the preface, the authors reflect that the 1940's were notable for the increasing sophistication of surgical and radiotherapeutic techniques, the 50's saw the trend towards methods of earlier diagnosis, the 60's heralded developments in cell physiology and kinetics for chemotherapy, radiation physics, tumour immunology and epidemiological studies to select high risk patients. The 1970's may be known as the "decade of therapeutic translation" when the insights derived can be applied.

The introduction covers the statistics of incidence, site, stage at presentation and the factors which influence the outcome. Known aetiological factors and the principles of diagnosis including cytology, histology and radiological methods are discussed. This section is well illustrated with photomicrographs and contains much useful information based on personal experience.

The principles of radiation therapy are covered in a broad way dealing with intracavitary and external radiation techniques. This is a short, factual chapter summarizing the art, providing the pros and cons of various treatments, giving dosages but avoiding detailed physics and radiotherapy techniques. I did not find any reference to afterloading techniques which can be so useful in reducing the exposure to staff and which in this country are becoming increasingly popular.

There is a chapter dealing with the principles of chemotherapy which, in addition to basic principles, includes reference to the dosages which are most often used in gynaecological malignancy. These are classified in the usual way based on their chemistry but there is also reference to the phases of action in relation to cell cycle theory. There is a particularly useful table of the characteristics and properties of the various stages of the cell cycle which makes a convenient summary of our present understanding.

Chapters then follow dealing in full detail with the common gynaecological cancers. These cover the usual aspects such as incidence, aetiology, investigation, staging, histology, management and the results of various forms of treatment. All these chapters are very well illustrated and the views expressed are very representative of current practice. This will be of considerable value to those studying for higher examinations in radiotherapy as well as gynaecological surgery.

In addition to the more common neoplasms, the authors deal with sarcomas and various gestational trophoblastic neoplasms. The chapter about the latter covers hydatidiform mole and chorio-carcinoma in a way which offers sound guidance to the clinician. It is very good to see a section on pain included in the book. This discusses the neurological pathways involved as well as the various theories of pain, before giving details of the different analgesics, antidepressants and surgical operations for control of pain.

As well as a useful account of menopausal problems there is a section on the endocrinological aspects of gynaecological cancer. This includes the physiological processes involved and also the production of hormones in certain pathological states, for example by tumours. Current views on the metabolism of hormones in target tissues and the present theory of the roles of receptor sites in breast cancer are included for completion. Breast cancer is usually not included in works on gynaecological cancer and understandably is not covered in this volume.

There is a particularly interesting chapter on basic clinical immunology for the gynaecologist. This covers this very complex topic in a concise and readable way. It was thoughtful to include a glossary of immunological terms which will be greatly appreciated.

The volume closes with chapters on epidemiology and biostatistics. It is an extremely well prepared work covering the subject and a great many more related problems, in a concise and informative way. It is well illustrated throughout and fully indexed. It can be highly recommended to radiotherapists and gynaecologists.

B. Hale.

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A less empirical method of representing megavoltage beams for use in rapid radiotherapy dose calculations

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ABSTRACT

A large number of initial measurements are needed for accurate computation of radiotherapy dose distributions directly from stored data on the dose distributions of single radiation beams. Because of this, interest has been shown in alternative methods which use empirical formulae to represent the dose distributions of single beams. These can be easier to implement but are less directly related to measured quantities and may be of limited validity. A method of representing radiotherapy beams is proposed which closely approximates their radiation physics, in order to calculate the dose at any point by a simple algorithm directly from a small number of initial dose measurements. The method is of wide validity, probably including all megavoltage radiations for which Compton scattering is the dominant interaction in tissue. The accuracy of the method is demonstrated by application to an 8 MV linear accelerator and a cobalt 60 machine.

In computer programs used to assist radiotherapy planning, the mathematical representation of megavoltage beams has been achieved mainly in two ways. In what may be called the bulk storage method, dose measurments on beams of a limited number of sizes are made and stored as a file on magnetic tape or disc (Bentley and Milan, 1971). For calculation of the dose at a point in a beam, interpolation is performed on the appropriate data extracted from the file. This method has the advantage of speed (as little as two or three seconds per beam) and a direct relationship between measured and calculated doses. It has been the method of choice for interactive programs. However, the penalty which has been paid for these advantages is the labour involved in the preparation of a reliable data file calling for some 15000 to 20000 measurements per treatment machine. It is mainly because of this that interest has grown in another method using empirical formulae (Kornelson and Young, 1975; Thomas and Haybittle, 1975).

In the method of empirical formulae, mathematical functions are proposed which model megavoltage beams in such a way that the number of adjustable parameters is minimized. The values of most of the parameters appropriate to a given treatment machine must be determined by comparison of the predictions of the model with measurements of the dose distribution. A set of values is chosen for the parameters and the distribution is calculated using the empirical formulae. The parameters are then adjusted to improve agreement between the calculated and measured distributions. This procedure is repeated a number of times.

The empirical formula method of representing megavoltage beams has limitations.

1. Because the formulae are chosen empirically rather than on strictly physical grounds, the range of validity is indeterminate. It is always uncertain whether formulae used for one machine will give an acceptable fit to the measured doses over the whole operating range of a similar but different machine. Extensive checking is therefore required which calls for more data on dose distribution in the beam than would appear necessary at first glance.

2. Functions which are chosen so as to minimize the number of adjustable parameters lead to expressions which cannot be evaluated quickly in a computer program. For example exponentials and non-integral exponents take longer to evaluate than the interpolations used in methods involving storage of beam data.

3. The parameters are of no interest in themselves. Their determination is an unnecessary stage between the measurement of dose at selected points and the computation of dose at other points in the beam. The empirical formulae impose on the calculated doses a certain form which may or may not correspond with reality. The relationship between measured and calculated doses is thus less direct.

To summarize, in moving from bulk data storage to empirical formulae, easier implementation has been gained at the cost of a direct relationship between calculated and measured doses. In the present work the physics of radiation beams is closely followed to calculate the dose at any point by a simple method from a small number of dose measurements. It is hoped in this way to restore the close connection between measured and calculated doses which is the advantage of the bulk storage method, without incurring penalties in ease of implementation or speed of execution. The method chosen parallels previous work using scatter-air ratios (Cunningham, 1972; Jayaraman, 1970) and takes advantage of rectangular beam geometry to simplify calculations.

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A LESS EMPIRICAL METHOD

Consider the absorbed dose $A(r, d, e, f)$ at point P in Fig. 1. P is in a rectangular field of megavoltage radiation of size $b \times w$ with equivalent square field of side e (e, b and w are measured at the nominal SSD f). It is at depth d (measured along the central axis) on ray r (measured in the same way as e, b and w) along a line AB which bisects the field. The SSD and depth measured along the ray are f' and d'. $A(r, d, e, f)$ can be divided into primary and scatter components ($D(r, d, e, f)$ and $S(r, d, e, f)$ respectively. The primary component is due to photons from the source of radiation of which secondary electrons cause energy deposition at P. The scatter component arises from secondary electrons of photons which are generated when primary radiation is scattered within the irradiated medium. On the central axis the separation of primary and scatter components can be recognized easily.

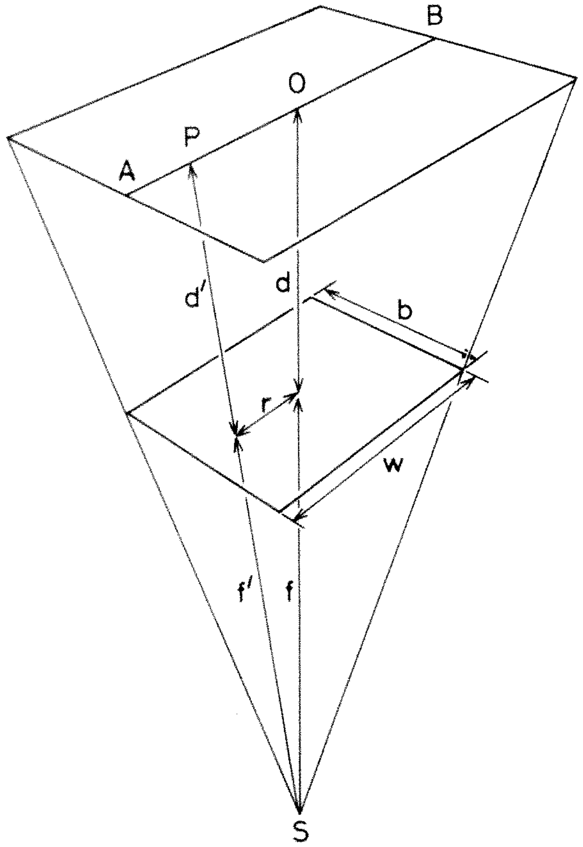


FIG. 1.
Geometrical quantities in the radiation field.

The primary component is identified as the absorbed dose on the axis of a beam so narrow that practically all scattered photons leave it—"zero field size".

$$A(o, d, o, f) = D(o, d, o, f) \quad . \quad . \quad . \quad . \quad (1)$$

The scatter component is responsible for the increment of absorbed dose which occurs if the field size is increased from zero. Thus the primary component on the central axis is determined by extrapolation of the central axis absorbed dose to zero field size (see also approximations section). The value so obtained can then be subtracted from the absorbed dose for finite field size giving the scatter component on the central axis for that size.

$$S(o, d, e, f) = A(o, d, e, f) - A(o, d, o, f) \quad . \quad . \quad (2)$$

Absorbed dose is tabulated for different depths and field sizes relative to its value at the depth of maximum dose in a 100 mm square field, *i.e.* $A(o, p, 100, f)$ is set to unity where p is the depth of the maximum. The table is transformed to infinite SSD by extraction of an inverse-square factor, *e.g.*

$$A(o, d, e, \infty) = A(o, d, e, f) \times (f+d)^2/(f+p)^2$$

Such a table can give central axis values of the primary and scatter components for all needed depths, field sizes and SSD's by linear interpolation or extrapolation and restoration of inverse-square factor.

Primary component

The primary component at the point P (Fig. 1) in a flat field is now considered. (The field is taken to be flat if the kerma rate measured in air is independent of position in planes normal to the central axis.) Points unaffected by the shadow of the collimator have a primary component $D(o, d', o, f)$ equal to the central axis value for depth d' and SSD f. The primary component in the penumbra region can be represented by its ratio $Q(r, d, w, f)$ to the unshadowed value.

$$D(r, d, e, f) = D(o, d', o, f)\, Q(r, d, w, f)$$

Since the primary radiation is unscattered prior to the event which causes energy deposition at the point of interest, it must travel in straight lines from the source. This determines the way in which the profile of the primary radiation penumbra changes with depth. The width scale of the profile expands with depth in proportion to distance measured from a point near the distal end of the collimator. (The distance between this point and the source defines the position of what will be called the effective level of collimation.) However, a line passing through a median line of the source and through the effective edge of the collimator marks the position of a half-central axis point of the primary radiation at any depth. These geometrical relationships ensure that measurement of the profile of the primary radiation at one depth fixes it for all depths if the effective level of collimation is known.

The absorbed dose deposited by the primary radiation does not follow precisely the same geometrical pattern. The absorbed dose profile is a smoothed copy of the radiation profile because of the range of the secondary electrons from photon interactions. It is shown in the section on secondary electron range, however, that the relationship between primary radiation profiles at different depths also holds for the associated absorbed dose profiles, with sufficient accuracy for radiotherapy planning over a wide range of beam energies. It is further shown in the succeeding section that in most cases the effective level of collimation can be approximated by the position of the source. This reduces $Q(r, d, w, f)$ to $Q(r, w)$ since in ray, depth co-ordinates the direct penumbra profile may be considered independent of depth and SSD. For a well designed and adjusted collimator the primary profile is independent of the field width w if r is measured relative to the edge of the field.

$$Q(r, w) = P(t)$$

where $t = |r| - w/2$ and the primary component becomes

$$D(o, d', o, f)\, P(t).$$

This profile can be estimated with very little contamination from the scatter component by measurement in a water phantom at the depth of maximum dose using a small ion chamber. A method of refining this estimate to remove remaining scatter contamination is given in the section on measurement of $P(t)$. Thus a table of $P(t)$ versus t can be compiled and $P(t)$ for arbitrary t obtained by interpolation.

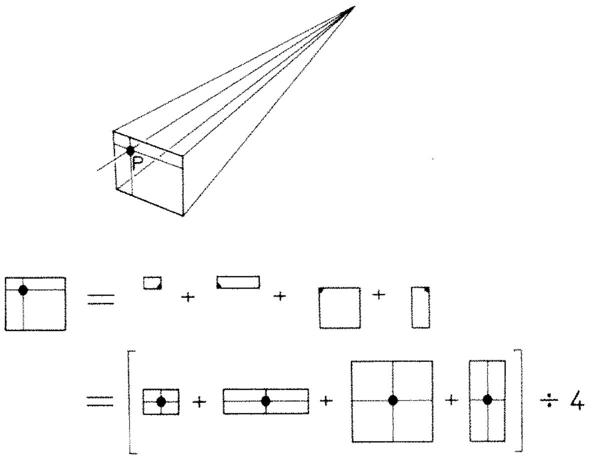


FIG. 2.
Area summation.

Scatter component

The scatter component at an off-axis point due to a rectangular beam can be expressed in terms of central-axis values alone by invoking an area summation principle (Day, 1950). In Fig. 2 the scatter component at P is divided into contributions from four partial rectangles. Each of these is then quadrupled to put P on the central axis. The equivalent square of a quadrupled rectangle can be calculated and the central-axis scatter component found. The scatter component at P is therefore just a quarter of the sum of the central-axis scatter components of the quadrupled rectangles (see area summations). For points on the bisecting line of the field (*APB*, Fig. 1) at present under consideration only two different quadrupled rectangles arise. If the effective field size at nominal SSD is $b \times w$ the two partial rectangles have sides b, $w+2r$ and b, $w-2r$ where r is the ray co-ordinate of P. Their equivalent squares e_+, e_- can be approximated by use of the relation $e_\pm = b(w \pm r)/(|b| + |w \pm r|)$ adapted from Worthley 1966). The scatter component at point P is then given by

$$S(o, d', e_+, f)/2 + S(o, d', e_-, f)/2 \quad . \quad . \quad . \ (3)$$

subject to the definition,

$$S(o, d, -e, f) = -S(o, d, e, f) \quad . \quad . \quad . \ (4)$$

for all d, e and f.

Total absorbed dose at point P is equal to the sum of the primary and scatter components as determined above,

$$D(o, d', o, f)\, P(t) + S(o, d', e_+, f)/2 + S(o, d', e_-, f)/2$$

or by substitution from equations (1) and (2),

$$A(o, d', e_+, f)/2 + A(o, d', e_-, f)/2 - (1 - P(t))\, A(o, d', o, f) \quad . \quad . \quad . \quad . \ (5)$$

subject to the equivalent of equation (4).

$$A(o, d, -e, f) = 2A(o, d, o, f) - A(o, d, e, f) \quad . \ (6)$$

All the terms in (5) can be obtained from tables of $A(o, d, e, \infty)$ and $P(t)$.

Wedge fields

For a number of reasons fields may be used which are not flat as previously defined. Here any variation is considered equivalent to the effect of a wedge oriented parallel to APB (Fig. 1) with lines of constant attenuation perpendicular to this direction. Such uneven fields are described by the factor $W(r)$ by which the primary component is changed relative to a flat field at a point with ray co-ordinate r. $W(r)$ can be measured in air using a small ion chamber with a cap just large enough to give secondary charged-particle equilibrium. (Alternatively $W(r)$ for the unwedged beam can be measured by the method described for $P(t)$ and then the wedged values determined by the ratio of wedged and unwedged doses measured at the same point in a water phantom). $W(r)$ can therefore be calculated when needed by interpolation in a table of measured values of $W(r)$ as a function of r. For all radiations investigated so far it has been sufficiently accurate to assume that the total absorbed dose at a point is modified by the factor $W(r)$ in the uneven field.

In summary, the measured dose data required to represent all the fields produced by a treatment machine consist of a table of central-axis absorbed dose as a function of depth and field size, a table of the profile of primary absorbed dose in the penumbra for rays near the edge of a field and a table of the factor $W(r)$ for rays covering the full width of fields for all wedge states (including no wedge).

Approximations

Important approximations made in the present method are examined and expressions are derived for estimating errors caused by them. Examples are given to illustrate the range of validity as far as possible.

Secondary electron range

The penumbra of the absorbed dose deposited by the primary radiation is caused partly by the penumbra of the primary radiation itself and partly by smoothing of the edges of the primary beam by secondary electrons. These vary in different ways with depth. As stated earlier, the width of the penumbra of the primary radiation increases with depth in accordance with rectilinear propagation from the source. However, the contribution from secondary electron smoothing is nearly depth-independent because the quality of megavoltage radiation varies very little with depth. In the section on the primary component it was assumed that the penumbra of primary absorbed dose increases with depth in the same way as the primary radiation penumbra. Since the primary absorbed-dose penumbra is measured at or near the depth (p) of maximum dose the effect of secondary electron smoothing will be overestimated at greater depths. The greatest error which this can possibly cause is an overestimate of the primary penumbra width by a factor $(f+d)/(f+p)$. This maximum error arises if the primary radiation beam has perfectly sharp edges, all the penumbra being generated by secondary electron smoothing.

Errors arising from incorrect width of the penumbra vary in importance according to the position considered within the penumbra and the maximum error occurs at a point which depends on the shape of the penumbra profile. However, for most shapes the maximum error occurs near the 25 and 75 percentage points which lie at each end of the steepest part of the profile. If these points are a distance $2v$ apart the overestimate of the penumbra width results in a positional error of approximately $v\ (d-p)/(f+p)$ for this region of the profile. In Table I the distance $2v$ between the 25 and 75 percentage points of a penumbra generated by secondary electrons only is estimated for the case of monochromatic photons. Also an estimate of the most serious positional error is given for 1000 mm SSD and 200 mm depth. This varies from 0·1 mm for photons of energy 1 MeV to 0·5 mm at 10 MeV. These estimates were obtained as follows. The mean energy of secondary electrons from Compton interactions was calculated from the ratio of absorbed and total cross-sections. The emission angle θ and the half-value depth h for the absorbed dose due to electrons of this mean energy could then be

TABLE I

Contribution of secondary electrons to penumbral width

Photon energy MeV	Mean Compton electron energy MeV	Emission angle degrees	Half-dose depth mm	Smoothing width (25–75%) mm	Positional error (1000 mm SSD, 200 mm depth) mm
1	0.44	30	1.5	0.5	0.1
2	1.07	28	3.6	1.1	0.2
3	1.75	24	5.8	1.5	0.3
5	3.11	20	10.4	2.3	0.4
10	6.74	14	22.5	3.5	0.5

determined. h was approximated by 3·3 mm per MeV of electron energy. Half this depth was taken as an estimate of the median displacement of absorbed dose away from the site of interaction. Only the component of the displacement which carries energy across the edge of the radiation beam is of interest. On average this is 2 $\sin\theta/\pi$ times the displacement. Twice this component was taken as an estimate of the width v between the 25 and 75 percentage points of a penumbra caused entirely by secondary electron smoothing. Thus $v=2h \sin\theta/\pi$.

Effective level of collimation

In the section on the primary component it was assumed that the effective level of collimation may be approximated by the position of the source. This approximation is not essential but is valuable because of the computational simplicity which it allows. However, it gives rise to underestimation of the primary penumbra width by a factor

$$a=\frac{(f+d)\ (f-c+p)}{(f+p)\ (f-c+d)}$$

at a depth d where c is the distance between the level of collimation and the source. As in the previous section, the most serious error occurs at approximately the 25 and 75 percentage points of $P\ (t)$. If $2b$ is the distance at depth d between those points, the positional error there is approximately $(1-a)\ b$. Applying this to a case which is unfavourable to the approximation, having $f=600$ mm, $p=5$ mm, $c=300$ mm and $2b=10$ mm, the most serious position error from this cause at a depth of 200 mm is less than 1 mm.

Measurement of P (t)

The penumbra profile measured at peak depth $(P'\ (t))$ as described in the section on the primary component is not entirely free from scatter contamination. In order to determine accurately the profile of the penumbra of the primary radiation alone $(P\ (t))$, it is desirable to calculate this contamination and subtract it. This is done by the following method.

First the profile $P'\ (t)$ is used to determine the size of the field in which it was measured according to the definition given in the following section (as opposed to the nominal size). When this field size has been established the scatter component at any point along the line of measurement of $P'\ (t)$ can be calculated by the method mentioned in the section headed scatter component. The scatter component can then be subtracted from $P'\ (t)$ to obtain $P\ (t)$, the penumbra shape for the primary component alone. If the size of the field used to measure $P'\ (t)$ is re-determined using the newly found $P\ (t)$ and the definition as detailed in the section, area summations, a slightly different value may be obtained. However, it is unneccessary to redetermine the scatter contamination as it is a small correction and does not depend strongly on the field size.

Area summations

In calculating the scatter components at any point from central axis values, the boundaries of the field and of partial rectangles were treated as sharp. In practice field boundaries are not marked by sharp lines but by gradual transitions due to the primary penumbra. It is thus necessary to choose a definition of field size which takes this into account. Clearly the definition must ensure that the primary penumbrae of two fields, nominally joined along a line, sum together to give the same total area under the curve of absorbed dose versus distance normal to the line, as would be obtained from a single field which combined the area of the two fields (Fig. 3). In practice this definition puts the nominal edge of the field very close to a point for which the total absorbed dose is 50% of the central axis value.

It is implicit in this method of combining fields of different sizes that the data on the fields to be combined refer to the same central axis primary component. It has been pointed out (Cunningham, 1972) that scattering from the collimator can generate a spurious contribution to the "primary" component which, moreover, may vary with field size. However, it has been found unnecessary to take this into account in the present work.

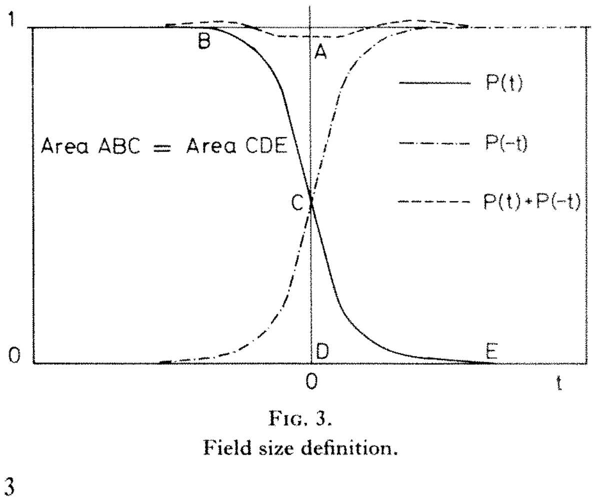


FIG. 3.
Field size definition.

TABLE II

Input dose data (8MV, 1000 mm SSD)

Central axis absorbed dose
mGy (per Gy at 20 mm depth in 100 mm nominal square field)

Depth mm	Equivalent square (mm nominal size)				
	0	50	100	150	200
0	72	101	150	209	247
5	627	700	750	796	825
10	815	892	930	964	985
15	869	941	978	1002	1016
20	896	966	1000	1020	1031
30	870	942	975	995	1005
60	749	819	855	878	892
90	628	706	745	776	789
120	522	602	645	673	691
150	442	514	560	587	608
180	360	440	485	510	531
210	313	377	420	446	464
240	264	322	360	383	402
270	220	278	315	336	355
300	197	237	270	296	309

Primary absorbed dose penumbra profile
$P(t)$ in mGy (per Gy on central axis) for points defined by ray co-ordinate t (mm from nominal edge of field at nominal SSD)

t	−20	−15	−10	−5	0	5	10	15	20
$P(t)$	1000	998	998	993	947	617	139	20	5

Wedge profiles
$W(r)$ in mGy (per Gy on unwedged central axis) for points defines by ray co-ordinate r (mm from central axis at nominal SSD)

r	Wedge angle			
	0 deg	30 deg	45 deg	55 deg
−60	1000	920	900	1000
−50	1000	865	849	906
−40	1000	818	805	813
−30	1000	775	758	737
−20	1000	748	699	673
−10	1000	719	662	615
0	1000	692	627	565
10	1000	675	596	531
20	1000	665	574	497
30	1000	653	552	474
40	1000	647	532	452
50	1000	642	512	441
60	1000	642	493	441

TABLE III

Input dose data (^{60}Co, 800 mm SSD)

Central axis absorbed dose
mGy (per Gy at 5 mm depth in 100 mm nominal square field)

Depth mm	Equivalent square (mm nominal size)				
	0	50	100	150	200
0	178	190	200	205	209
2	765	817	860	871	889
4	885	949	1000	1024	1048
6	885	949	1000	1024	1048
30	739	818	897	935	958
60	548	658	754	795	828
90	408	517	618	667	704
120	310	409	500	550	590
150	225	314	402	451	486
180	175	248	322	366	404
210	128	192	259	299	332
240	104	152	206	244	271
270	80	122	167	198	224
300	57	95	131	161	182

Primary absorbed dose penumbra profile
$P(t)$ in mGy (per Gy on central axis) for points defined by ray co-ordinate t (mm from nominal edge of field at nominal SSD)

t	−20	−18	−16	−14	−12	−10	−8
$P(t)$	1000	999	997	994	991	985	960
t	−6	−4	−2	0	2	4	6
$P(t)$	877	760	629	489	359	216	114
t	8	10	12	14	16	18	20
$P(t)$	49	22	13	9	8	8	8

Wedge profiles
$W(r)$ in mGy (per Gy on unwedged central axis) for points defined by ray co-ordinate r (mm from central axis at nominal SSD)

Wedge angle 0 deg

r	$W(r)$	r	$W(r)$
−110	980	0	1000
−100	985	10	1000
−90	987	20	999
−80	990	30	998
−70	992	40	998
−60	994	50	996
−50	996	60	994
−40	998	70	992
−30	998	80	990
−20	999	90	987
−10	1000	100	985
		110	980

Zero field size extrapolation

Extrapolation to zero field size of the central axis absorbed dose presents some difficulties. The smallest field size at which measurements can easily be made is about 30 mm square and it is not clear what form the extrapolation should take at smaller sizes. However, the method of extrapolation is not critical because the absorbed dose given by (5) is insensitive to small errors in the value of $A(o, d, o, f)$ (the central axis absorbed dose at zero field size) almost everywhere. This can be seen by considering each of three regions of the field identified by their value of $P(t)$.

(i) Inside field away from edge, $1-P(t) \ll 1$, $e_- > o$.

$$D = A(e_+)/2 + A(e_-)/2 - (1-P(t))\,A(o) \quad . \quad . \ (7)$$

(abbreviating $A(o, d', e, f)$ to $A(e)$ etc.)

(ii) Outside field away from edge, $P(t) \ll 1$, $e_- < o$.

$$D = A(e_+)/2 - A(-e_-)/2 + P(t)\,A(o).$$

by substitution of (t) in (7).

(iii) Near edge, $P(t) \sim 0.5$, $|e_-| \ll |e_+|$.

$$D = A(e_+)/2 + (A(e_-) - A(o))/2 + (P(t) - 0.5)\,A(o).$$

In regions (i) and (iii) the contribution of the term containing $A(o)$ to the total dose is small. In region (iii) the contribution of such terms is small (or zero depending on the definition of the field size) when e_- is zero (edge of field). Between the edge and the other regions the propagation of errors from $A(o)$ to the total dose depends on the shape of $P(t)$. However, this region is the steep part of the penumbra where large errors in dose are equivalent to small lateral shifts.

Application of the method

The method has been applied using such suitable data as were available for an 8 MV linear accelerator (MEL SL75) and a cobalt machine (TEM Mobaltron). Sufficient data for representing the machines for this purpose by the present method appear in Tables II (8 MV) and III (Cobalt). In each case the primary penumbra profile was determined using data from the penumbra region of a profile measured at a depth of 20 mm in a field approximately 100 mm square. A correction was made for the scatter component by the method described in the section headed measurement of $P(t)$. To test the validity of this approach the penumbra of the cobalt machine (for which more detailed information was available)

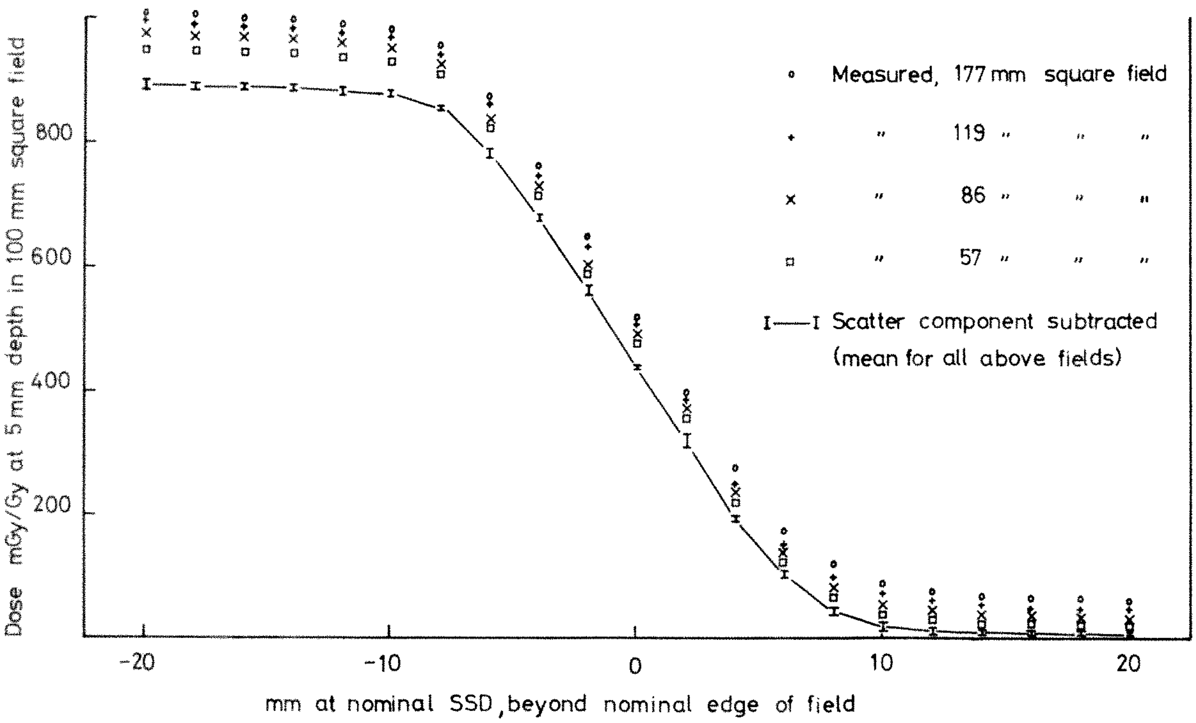


FIG. 4.

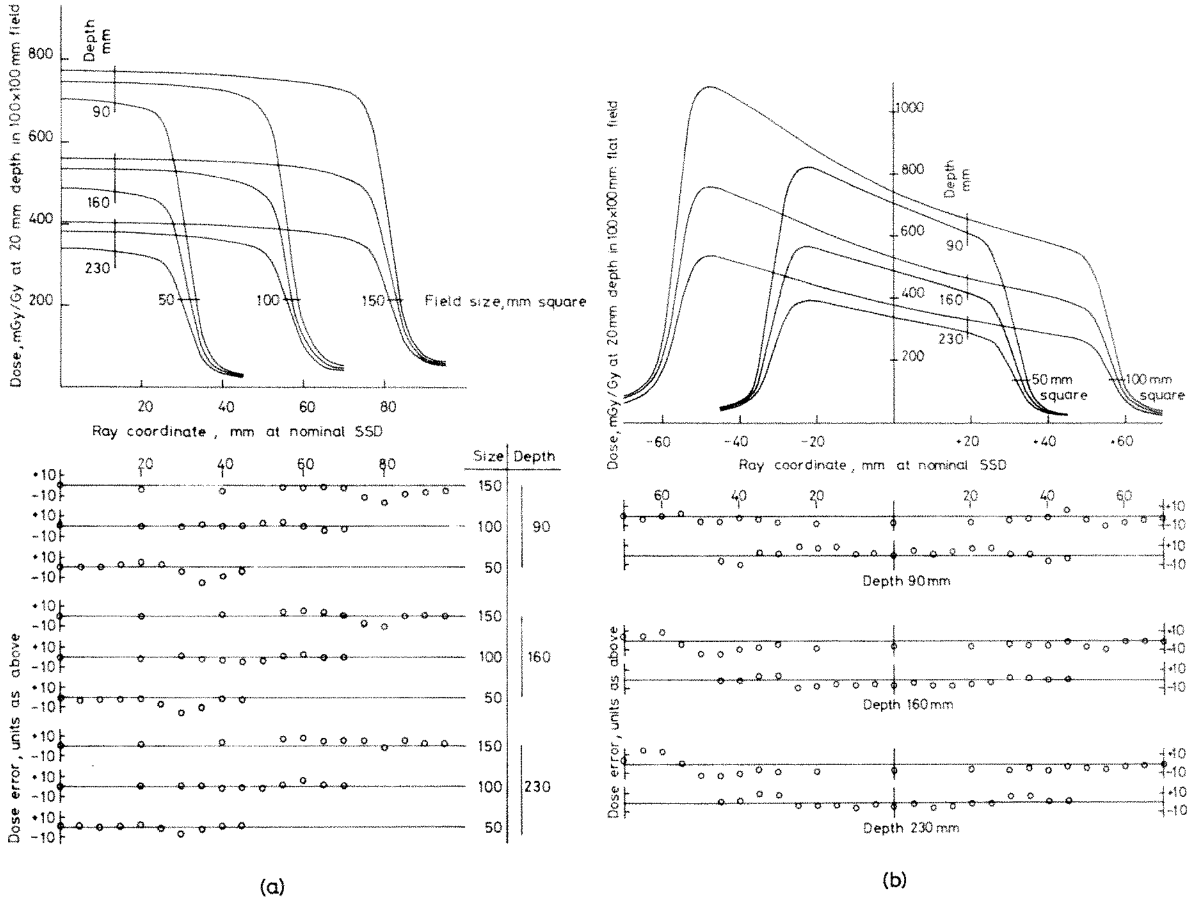
Penumbra region of 57, 86, 119 and 177 mm square ^{60}Co fields showing the total absorbed dose profiles measured at 20 mm depth and the mean and standard deviation of primary profiles obtained by subtraction of the scatter component.

was investigated closely. Profiles of fields of several sizes (57, 86, 119 and 177 mm square) were used to calculate the primary absorbed dose profile. Figure 4 shows all the uncorrected profiles and also the mean and standard deviation of the profiles obtained by correction for the scatter component. The small deviations of the corrected profiles confirm that the primary absorbed dose penumbra is independent of field size as suggested earlier.

The overall accuracy of the method of representation was tested by calculation of beam profiles for depths and field sizes for which measured profiles were available. For 8 MV, profiles of flat fields of nominal sizes 50, 100 and 150 mm square and 55 deg wedge fields of 50 and 100 mm square were calculated for depths of 90, 160 and 230 mm. These are compared with measured profiles in Figs. 5a and b. For cobalt 60, profiles of fields of sizes 57, 87, 119, 135, 176 and 199 mm square were calculated. Wedge fields were not included because the wedge data were available only in the form of isodose curves and although these can be adapted for use in the present method they are not suitable for a test of accuracy (Wilkinson and Redmond, 1975). For both machines, error histograms (Fig. 6) were compiled from all calculated points (weighted to give equal importance to each part of each field.) These show that fewer than 3% of calculated doses differ from measured values by more than 12 mGy (per Gy at peak depth in a 100 mm square field).

DISCUSSION

A case has been made on theoretical grounds which suggests that the present method of representation is valid over the range of megavoltage beam energies for which Compton scattering is dominant in tissue. The evidence on the practical application of the method does not contradict this view.



(a) (b)

FIG. 5.

Calculated profiles of 8 MV linear accelerator fields (upper) and differences between calculation and measurement (lower) at depths of 90, 160, 230 mm for 1000 mm SSD. (a) 50, 100, 150 mm square flat fields. (b) 50, 100 mm square wedge fields.

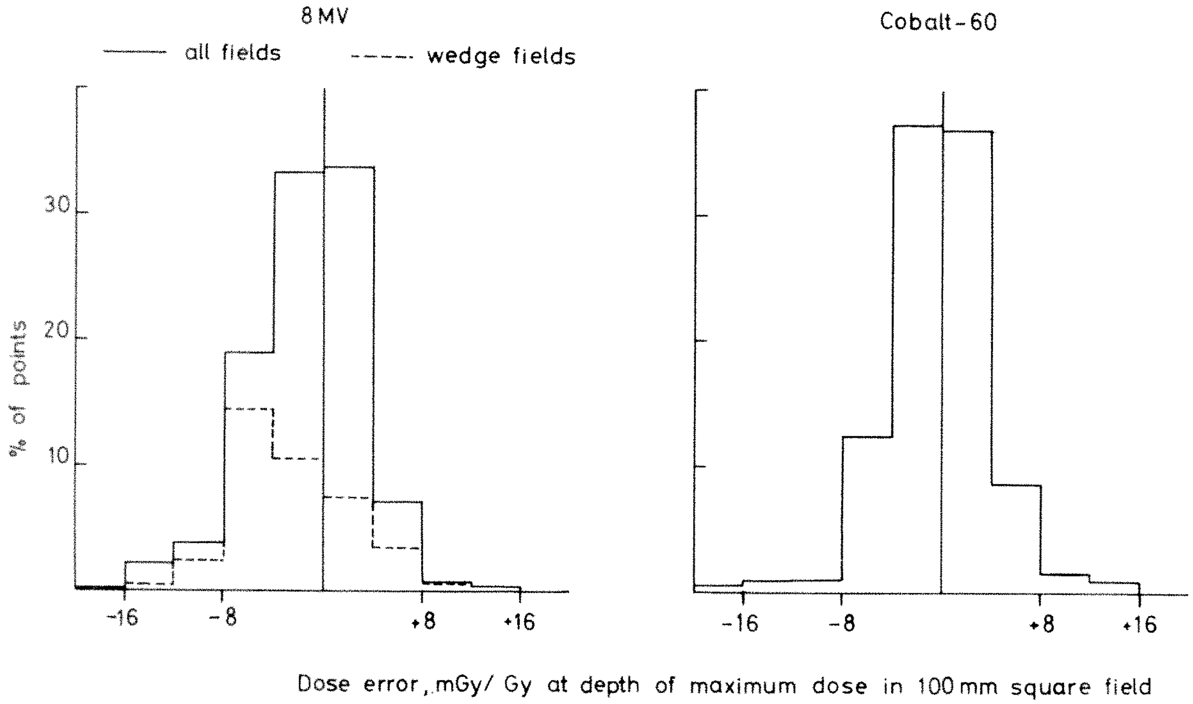


FIG. 6.

Histograms of differences between measured and calculated doses for 8 MV X rays and cobalt-60 gamma rays.

The method can be implemented using dose measurements from relatively few points in the beam (less than 140 in the present examples). In practice all or most of these dose data will be required to implement manual planning on the same machine. The doses at other points in the beam are calculated directly from the measured doses.

The method is suitable for rapid dose calculation in a computer program. A Fortran version has recorded execution times of approximately 12 seconds per field (Data General Nova) and two seconds per field (Data General Eclipse, hardware floating-point arithmetic) for calculation of teletherapy dose distributions.

Although the present work is restricted to doses in a plane including the central axis the method is inherently three dimensional. Very little (if any) additional data would be required to calculate doses in other planes.

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The value of a tracer dose in predicting the kinetics of therapeutic doses of ^{131}I in thyrotoxicosis

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ABSTRACT

The kinetics of tracer doses of ^{131}I, assessed by measuring uptake and effective half-life, correlate well with the kinetics of therapy doses. The effective half-life was measured using thermoluminescent discs fixed to the patients' anterior neck surface. This method gives results comparable with those obtained using an uptake probe, and met with a good response by the patients. Using the kinetics of the tracer dose to assist prescription of radioiodine therapy would considerably reduce the spread of absorbed doses to the glands of a group of patients. The case for attempting more exact dosimetry in this field is reviewed.

Following the introduction of radioiodine therapy for thyrotoxicosis several authors attempted to quantitate the radiation dose administered to the thyroid by monitoring the uptake and elimination of tracer and therapy doses (Blomfield *et al.*, 1951; Freedberg *et al.*, 1952; Silver, 1968; Malone, 1975). This practice was subsequently discontinued in many centres because of a feeling that there is little correlation between the kinetics of tracer and therapy doses or because there appeared to be no relationship between a physical dose measured in rads and the clinical outcome of therapy (Esselstyn and Crile, 1971; Werner, 1971; Silver, 1968; Beierwaltes *et al*, 1969).

Re-examination of the original published data on which both of the above conclusions have been reached demonstrates that they are inadequate to support either point of view. This statement will be justified in the discussion. Here it is sufficient to say that the original data prompted a new investigation of the relationship between the kinetics of tracer and therapy doses of radioiodine. This paper presents the results of the investigation and indicates that the degree of correlation present, though not perfect, is surprisingly good and possibly better than might be expected. Measurement of iodide kinetics was made with thermoluminescent discs which have previously been demonstrated to be sufficiently sensitive for this purpose at both tracer and therapy levels (Malone and Cullen, 1975; O'Connor *et al.*, 1978). However, the validity of half-life measurements made with them has not previously been demonstrated in a significant number of patients. Therefore this method is validated here since the clinical data presented are dependent on it. These results indicate that more refined dosimetry of radioiodine therapy may be both practical and possible. Hence the question of whether or not such measurements are likely to be helpful in predicting the outcome of therapy is raised in the discussion.

MATERIALS AND METHODS

Patients (for validation of thermoluminescent method)

Sequential patients referred for radioiodine therapy of hyperthyroidism or thyroid carcinoma were studied. The doses administered ranged from 5 μCi to 150 mCi of ^{131}I. The effective half-life of the administered dose was monitored using both thermoluminescent discs and uptake probes as described below. In all, the half-life was measured in 23 euthyroid and thyrotoxic patients and two patients with thyroid carcinoma.

Patients (for study of tracer and therapy iodide kinetics in hyperthyroidism)

Sequential patients scheduled to undergo radioiodine therapy for thyrotoxicosis were monitored. There were 31 patients, 17 with Grave's disease, 12 with multinodular goitre and 2 with single hot nodules. The dose of ^{131}I administered when tracer kinetics were being monitored was in the range 5 to 16 μCi, but was normally 9 μCi. Therapy doses were in the range 1 to 10 mCi. All doses were administered orally. When tracer and therapy kinetics were being compared the therapy dose was always given within one month, and frequently within two weeks of the tracer dose. During the intervening period no antithyroid drugs were used, although some patients were given Propranolol. No special precautions were taken to keep the iodine content of the patients' diet constant.

Measurement of uptake

Uptake of tracer doses was measured 24 hours after administration, using a scintillation counter with a 5 cm × 5 cm NaI(Tl) crystal. This was housed in a 6 cm diameter parallel-sided lead collimator, the leading face of the crystal being recessed 10 cm into the shielding. A standard containing a known fraction of the dose administered to the patient was counted in a neck phantom. The uptake of therapy doses was measured similarly except that the scintillation counter was replaced by one with a 2.5 × 2.5 cm crystal and a collimator with a pinhole aperture was used. This reduced the count rate to a level where errors due to dead-time did not occur.

Measurement of effective half-life

Effective half-life was estimated by measuring the thyroidal radioiodine content several times per week with the appropriate external probe or with thermoluminescent discs. The use of thermoluminescent discs for this purpose has been described elsewhere and will only be summarized here (Malone and Cullen, 1975; Malone *et al.*, 1976; Cullen *et al.*, 1976; O'Connor *et al.*, 1978). Finger sachets containing discs were placed reproducibly on the anterior neck surface, over the patient's thyroid, using Band-Aid dressings. Additional discs were placed on the calf to determine the background. For each reading the discs were left in position for 24 hours and then removed. Readings were obtained for the first three days after the dose was administered and thereafter two to three times per week. After an initial instruction period the discs were normally placed in position by the patients themselves and returned to the laboratory by hand or by post. However, when comparing tracer and therapy half-lives only data taken over identical periods of time were used. After being returned to the laboratory the discs were read on a Pitman 205–C digital TLD reader.

Dose calculations

Where figures are presented for absorbed dose in rads they have been calculated using the absorbed fraction method (Loevinger and Berman, 1968; Snyder *et al.*, 1969) and the decay scheme for ^{131}I published by Dillman (1969). Details of how this scheme was applied to the thyroid are presented elsewhere (Malone, 1979).

RESULTS

Figure 1 compares the effective half-life (T_{eff}) of ^{131}I in the thyroid determined with an external probe with that obtained using thermoluminescent discs. In all 25 cases are presented, consisting of a mixture of tracer and therapy patients. There is an excellent correlation (r=0.99) between the two methods. The total number of half-life determinations that have been collected to date using the thermoluminescent method is 91. Of these 63 were made by patients in their own homes, and only 2 of the 63 failed. The 28 measurements which were supervised in the hospital consist largely of those performed when the technique was being set up and validated. Clearly, from the failure rate of 2 out of 63, the response of patients to the method has been good and the level of co-operation high.

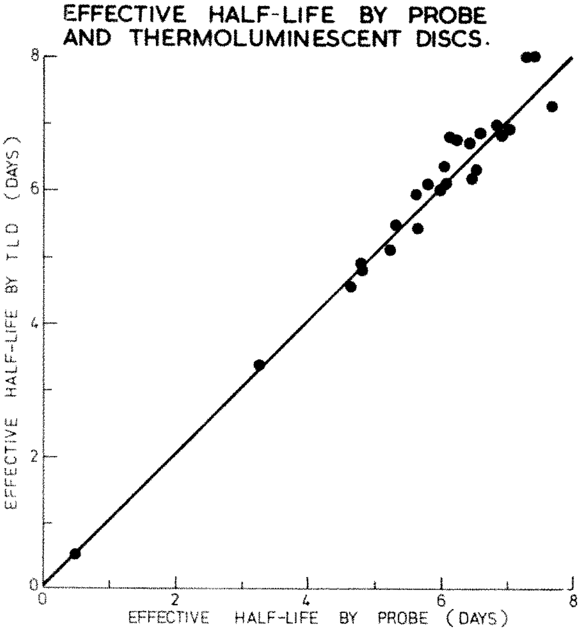

Fig. 1.

Effective half-life of ^{131}I in the thyroid determined by conventional uptake probe (abscissa) and by thermoluminescent discs (ordinate). All measurements were supervised by hospital staff.

In Fig. 2 the uptake of tracer and therapy doses is compared in 31 patients. There is an excellent correlation between the two sets of values (r=0.94) indicating, as is commonly accepted, that the uptake of the tracer dose is a good guide to that of the therapy one. Figure 2 also presents histograms of the tracer and therapy uptakes. The mean values and standard deviations are 67.1±14.8% and 64.4±15.3% respectively. Table I lists the number of therapy uptakes that lie within specified percentage ranges of the appropriate tracer value. Table I also lists data abstracted from Freedberg *et al.* (1952), and Blomfield *et al.* (1951). The combined results indicate that in 86% of cases the therapy uptake will lie within 15% of the value predicted by the tracer.

Figure 3 and Table II present comparisons of the effective half-lives of tracer and therapy doses of ^{131}I. Despite three points in which the therapy half-life is

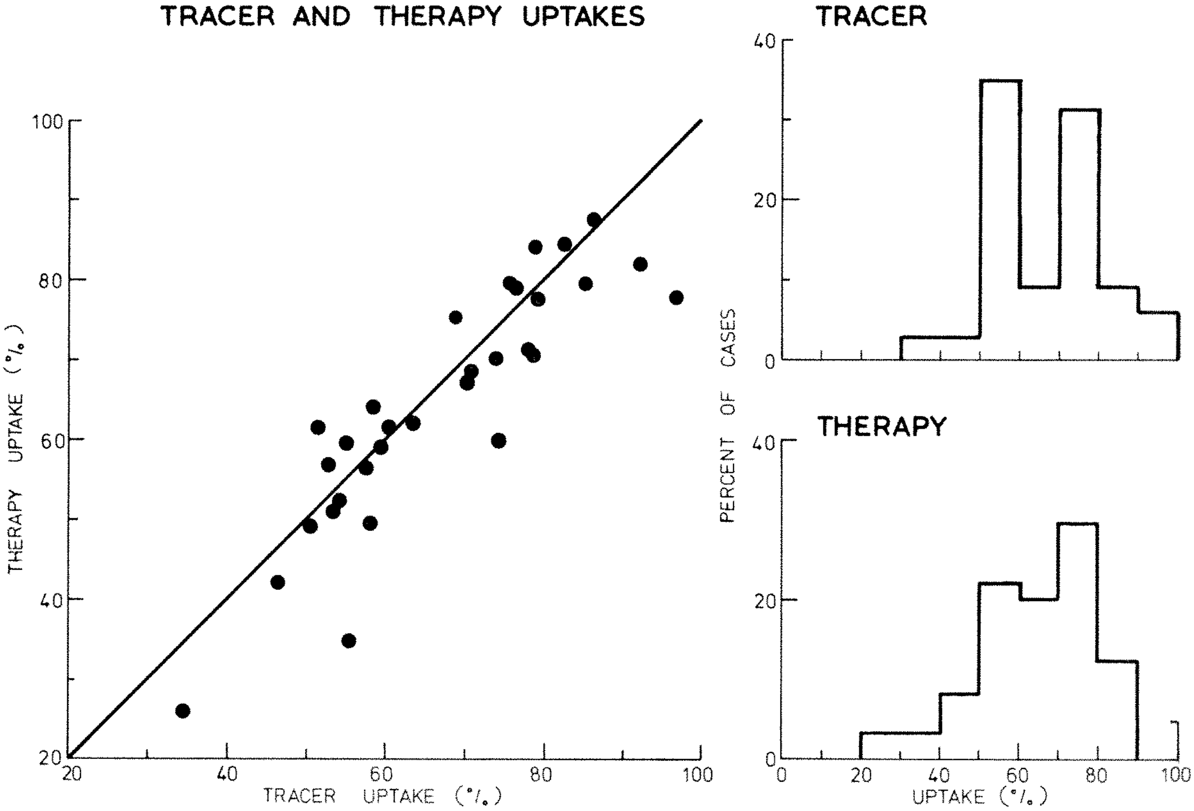

FIG. 2.

Twenty-four hour uptake of tracer and therapy doses of ^{131}I. The line on the left panel is the line of identity and does not represent a fit to the data points. The histograms on the right represent the distribution of uptake values.

noticeably shorter than that of the tracer (Fig. 3) there is a good positive correlation between the two values ($r=0.7$). In fact, Table II demonstrates that 81% of the therapy values lie within 10% of the value that would be expected from the tracer. Table II also lists data from Freedberg *et al.* (1952) and Blomfield *et al.* (1951), that support the existence of a correlation. The histograms of tracer and therapy effective half-lives in Fig. 3 show mean values and standard deviations of 6.3 ± 1.0 days and 6.2 ± 0.9 days respectively. The results of Freedberg *et al.* (1952) and Blomfield *et al.* (1951) are also plotted in Fig. 4.

Figure 5 presents histograms of the absorbed dose that would have been received by the populations described in Figs. 2, 3 and 4. A total of 92 cases is involved—31 from our data and 61 from the two references listed above. In all cases, a gland mass of 30 g has been presumed to allow direct intercomparisons of the effects of uptake and effective half-life alone. Three different modes of prescription are postulated. Administration of 4 mCi to all patients, regardless of their uptake and effective half-life, as shown at the top, results in doses that spread from 1000 to 14000 rad with a mean dose of 7400 rad. If the administered dose is corrected for uptake alone, and a target dose of 7400 rad is selected, there is a smaller spread in values (centre panel) but the distribution is biased and the mean dose is reduced to 6500 rad compared with the target dose of 7400 rad. Correction of the administered dose to take account of both uptake and effective half-life, and retaining a target dose of 7400 rad, further improves the shape of the distribution (bottom). The spread in values is slightly reduced and the mean dose is very close to the target, 7400 rad.

DISCUSSION

The data in Fig. 1 confirm the previous impression based on limited experience (Cullen *et al.*, 1976; Malone *et al.*, 1976), that thermoluminescent discs may be used to make relative measurements of the

TABLE I

DEVIATION BETWEEN VALUE OF R.A.I.U. DETERMINED DURING DIAGNOSIS AND THERAPY DURING THIS AND TWO OTHER STUDIES

Source	Deviation between diagnostic and therapy value (%)	No. of cases within deviation	% of cases
Present study 31 cases	5	13	42
	10	23	74
	15	26	84
	20	29	94
	>20	2	6
Freedberg *et al.* 53 cases	5	31	59
	10	39	74
	15	45	85
	20	48	91
	>20	5	9
Blomfield *et al.* 20 cases	5	6	30
	10	12	60
	15	18	90
	20	18	90
	>20	2	10
3 studies combined 104 cases	5	50	48
	10	74	71
	15	89	86
	20	95	91
	>20	9	9

TABLE II

DEVIATION BETWEEN EFFECTIVE HALF-LIFE DETERMINED DURING DIAGNOSIS AND THERAPY DURING THIS AND TWO OTHER STUDIES

Source	Deviation between diagnostic and therapy values (%)	No. of cases within deviation	% of cases within deviation
This study 31 cases	5	15	48
	10	25	81
	15	26	84
	20	28	90
	>20	3	10
Freedberg *et al.* 49 cases	5	16	33
	10	25	51
	15	31	63
	20	40	82
	>20	9	18
Blomfield *et al.** 12 cases	5	2	17
	10	2	17
	15	5	42
	20	8	67
	>20	4	33
3 studies combined 92 cases	5	33	36
	10	52	57
	15	62	67
	20	76	83
	>20	16	17

*$T_{\frac{1}{2}\,\mathrm{eff}}$ usually measured over a relatively short time period.

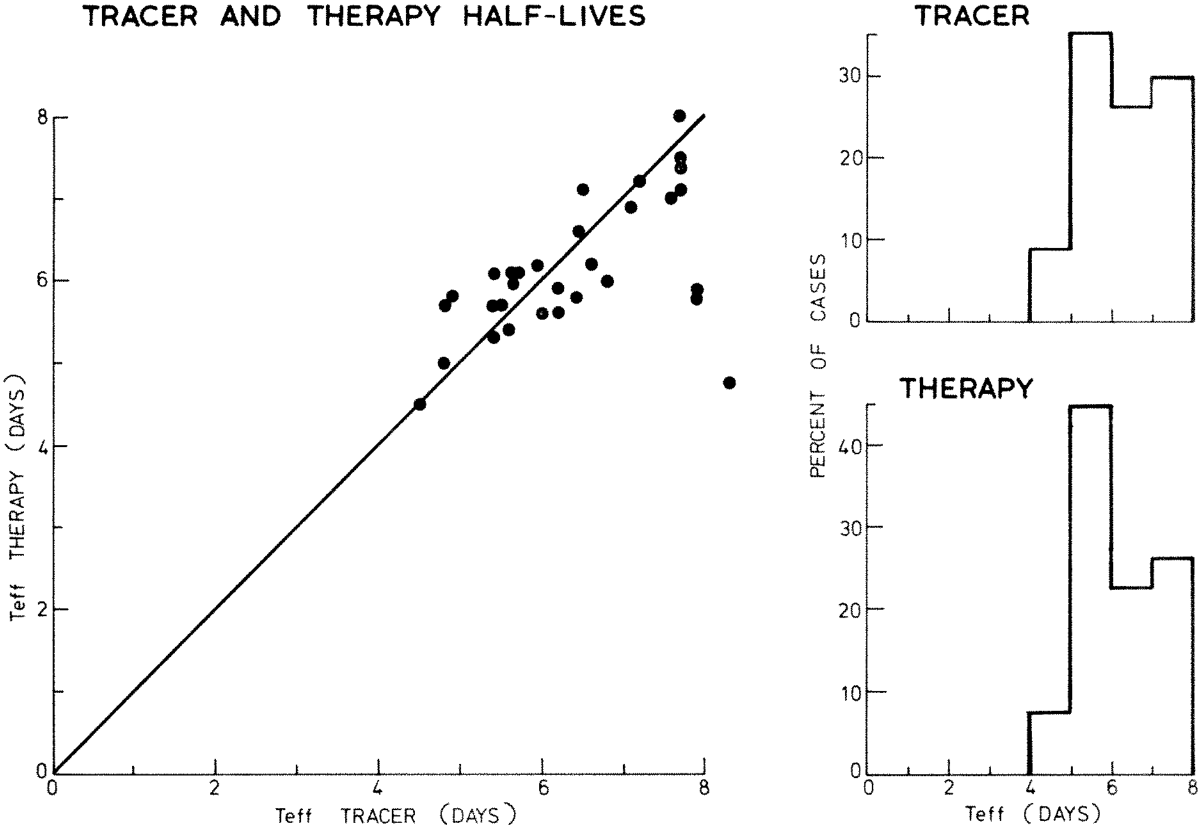

FIG. 3.

Effective half-lives of tracer and therapy doses of ^{131}I. The line on the left panel is the line of identity and does not represent a fit to the data points. The histograms on the right side represent the distribution of effective half-lives.

^{131}I activity in the thyroid. This method may now be accepted as a suitable alternative to conventional probe measurements for T_{eff}. One of the virtues of the method is its convenience in that it should allow half-life estimates without multiple hospital visits and should be capable of being applied by many patients in their own homes. To be successful in this regard the discs should not be sensitive to minor positional changes from day to day. *In vitro* experiments indicate that the discs are far less sensitive to small changes in position than would be expected with the exception of cases in which the thyroid is very large and superficial with widely separated lobes. Even in these cases the dependence of the discs' response on position can be reduced sufficiently by selection of a suitable configuration in which they may be applied (O'Connor *et al.*, 1978). The second requirement for successful operation of the technique at home is co-operation by the patient, and this was readily forthcoming. The 28 sets of measurements performed under the supervision of hospital staff were associated with setting up and validating the method, and under normal circumstances would have been performed by the patients at home. The two failures of the technique when it was applied by the patients themselves were due to: (a) an administrative error in one case, and, (b) to the patient undergoing radiological investigations with the discs in position in the other.

Figure 2 confirms the experience of other authors in finding a good correlation between the uptake of tracer and therapy doses of ^{131}I (Silver, 1968; Blomfield *et al.*, 1951; Freedberg *et al.*, 1952; Malone, 1975). The existence of such a correlation is routinely, though not universally, used in correcting the dose that will be prescribed during radioiodine therapy. In occasional patients there is a serious departure between the tracer and therapy values. These discrepancies cannot always be explained in terms of a specific identifiable cause, but are usually thought to be associated with medical treatment or alterations in dietary iodine (de Groot and Stanbury,

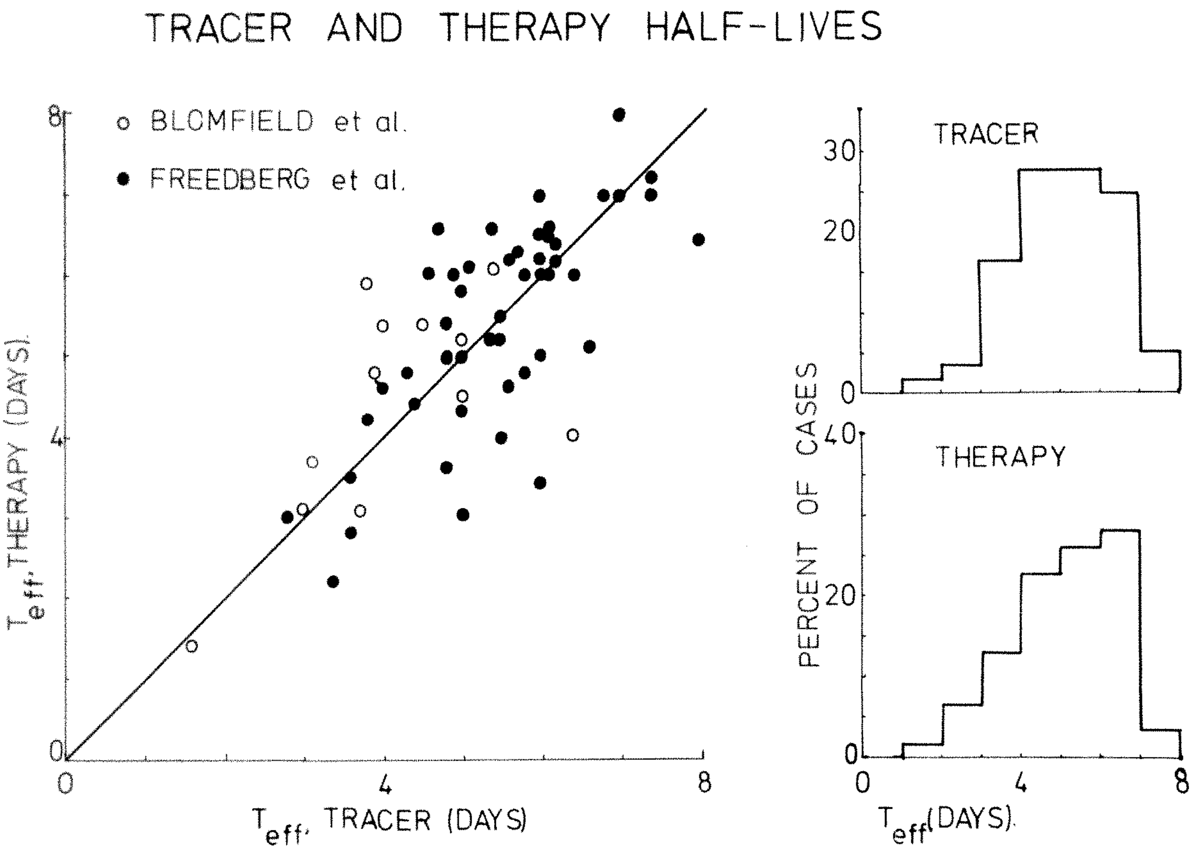

FIG. 4.

Effective half lives of tracer and therapy doses of ^{131}I in patients of Blomfield *et al.* (1951) and Freedberg *et al.* (1952). The line on the left panel is the line of identity and does not represent a fit to the data points. The histograms on the right side represent the distribution of effective half lives.

1975; Freedberg *et al.*, 1952). The fact that such discrepancies occur render it worthwhile confirming the uptake of the therapy dose if a quantitative dosimetry regime is being pursued. While these data confirm the existence of a correlation in individual patients, it is unlikely that uptakes obtained using conventional methods are sufficiently accurate for the purpose of dose prescription, as they are subject to large errors due to variations in geometry and tissue attenuation (O'Connor and Malone, 1978).

The data in Fig. 3 and Table II indicate that in most patients the effective half-life of a tracer dose is a reliable guide to that of a subsequent therapy dose, although in a small number of cases there is

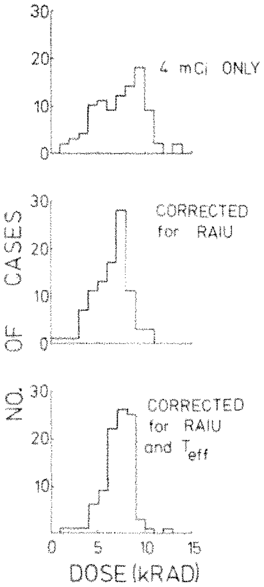

FIG. 5.

Distribution of dose to patients to whom 4 mCi of ^{131}I is administered (top). The centre and bottom panels are for patients in whom the target dose was 7400 rad and for whom the administered dose was corrected for uptake (centre) and uptake and effective half-life (bottom).

significant disagreement (Fig. 3.). A similar conclusion could be based on the data of Freedberg *et al.* (1952) and the possibility that such a correlation existed was inherent in the data of Blomfield *et al.* (1951) as shown in Fig. 4. Despite this, some workers have found the correlation between the effective half-lives of the tracer and therapy doses to be less convincing than that demonstrated here (Creutzig and Hundeshagen, 1976; Silver, 1968), and many authoritative sources are of the opinion that it is so poor that it would be of little use in prescribing the dose accurately (Silver, 1968).

As illustrated above, the data published in the open literature do not justify this opinion, and on the contrary, to some extent support the opposite conclusion. In the present study the strict limitation on medical treatment, and the relatively short time interval between tracer and therapy doses, may have contributed to the good correlation between their effective half-lives. It is possible that more rigid control of these variables and of dietary iodine may lead to further improvements in the correlation that can be obtained and contribute to explaining the reasons for the small number of outlying cases. In our experience, limitation of medical treatment for the two to four weeks between tracer and therapy doses has not lead to difficulties in the great majority of cases. However, medical supervision is required during the period for which treatment is withheld.

Some workers have taken an alternative approach to estimating effective half-life for dosimetry purposes. Instead of direct measurement of thyroidal ^{131}I the PB ^{131}I is measured at some known time such as 24, 48 or 72 hours after the dose is administered (Barandes *et al.*, 1973; Glanzmann *et al.*, 1975; Creutzig and Hundeshagen., 1976). From the PB ^{131}I the effective half-life is estimated using a nomogram or graphical relationship that has been established from previous experience. When averaged over large numbers of patients these relationships appear reliable, but they may be subject to substantial under- or over-estimation in individual cases (Creutzig and Hundeshagen, 1976). However, it is interesting to note that Barandes *et al.* (1973) have estimated by using the above method that in about 14% of patients the half-life is very short, of the order of two days.

In this paper, the problems associated with estimation of gland mass have not been considered. Even in experienced centres uncertainties in the value of the mass can lead to errors in the absorbed dose of a factor of two (Smith and Wilson, 1967). However, it is likely that the large number of new imaging techniques now available will reduce the uncertainties in estimates of mass (Rasmussen and Hjorth, 1974), and thereby contribute to greater refinements in dosimetry.

The data and discussion presented above indicate that it is likely to be technically possible to measure thyroidal effective half-life in a simple manner that involves sufficiently few hospital attendances to be acceptable. It also indicates that such data may be useful in prescribing a particular absorbed dose to the gland. However, the fact that dose estimates may be made relatively easily is of little consequence if widely held views on the variability of the radiobiological response of the thyroid are true (Silver, 1968; Werner, 1971; Becker and Hurley, 1971; Dworkin, 1971). In this context it is worth noting that the argument that the consequences of radioiodine therapy do not correlate well with dose to the gland cannot be sustained since, with few exceptions, dose has not been measured with sufficient accuracy to allow such conclusions to be drawn. In fact, much of the variability in response is likely to be attributable to the wide range of absorbed doses received by patients given apparently identical treatments by clinical standards (Fig. 5). Furthermore, it is probably inappropriate to seek a single dose-response relationship for the consequences of treatment, since different endpoints such as control of symptoms, reduction of hormone levels, induction of euthyroidism or hyperthyroidism may each have a distinct and quite separate relationship with absorbed dose. For example, the incidence of hyperthyroidism two years after therapy appears to be linearly related to dose (Malone and Cullen, 1976; 1977). Similarly, cell survival and some functional endpoints have been demonstrated to have relatively well defined dose-effect relationships in experimental animals or in tissue culture systems (Malone 1975; O'Connor *et al.*, 1979a, b; Greig *et al.*, 1970). Relationships for other endpoints such as induction of euthyroidism may be more difficult to identify and in some cases may have to take explicit account of extrathyroidal indices of the severity of the disease being treated, such as LATS levels, oxygen consumption and natural history, as well as the radiobiological properties of the gland. That such relationships have not been identified to date is not surprising since the absence of accurate techniques of dosimetry has been compounded by the lack of agreement on the most appropriate way to quantitate many of the above factors. Therefore, the fact that dose-effect relationships in this area have not been defined does not mean that it is impossible to do so provided account is taken of the physical and patho-physiological variables involved.

The absence of a method by which the outcome of therapy can be predicted in individual cases has lead some workers to administer ablative doses to all patients and to accept the known complication of hyperthyroidism (Esselstyn and Crile, 1971; Goldsmith, 1972). This renders management of the follow-up much simpler since all the patients may be placed on hormone supplements. However, such a procedure is not entirely free of hazard since ablative doses have been followed by recurrent thyrotoxicosis (Turner *et al.*, 1977) and large doses have been associated with an increase in the severity of exophthalmic complications (Kriss *et al.*, 1967). These problems, coupled with the undesirability of rendering patients dependent on hormone substitutes for life, make it worthwhile undertaking a search for methods of rendering the outcome of radioiodine therapy more predictable in individual cases in a limited number of centres.

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Doses to patients from pantomographic and conventional dental radiography

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ABSTRACT

The increasing popularity of pantographic dental radiography and particularly its recent use for routine screening of asymptomatic patients have prompted the NRPB to compare the risks to patients from this technique with those from more conventional dental diagnostic procedures. Pantographic equipment from seven manufacturers have been investigated along with five procedures for obtaining similar information using conventional dental X-ray sets. Lithium borate thermoluminescent dosimeters located at 141 sites in the head and neck of a Rando phantom have been used to measure the mean absorbed dose to organs of interest as well as the total energy imparted to the phantom. Relative values of the energy imparted by the various techniques provide an estimate of their relative somatic risk to the patient. Pantomographic techniques were generally found to impart less than half the energy to the phantom than that given by a conventional full-mouth periapical series conducted at 45 kV, and a similar amount of energy to four bitewing intra-oral films. The restriction of the frequency of pantomographic examinations to no more than once per year during adolescence and once per three to five years during adulthood has been shown to involve only a minimal increase in the risk of somatic injury to the patient.

Pantomographic dental radiography is a technique which in the last few years has become increasingly popular in dental practices in the United Kingom. Its introduction has led to a considerable increase in the number of patients who are examined radiographically and in the frequency with which these examinations are made on individual patients. This is evident from the number of claims recently submitted to the Dental Estimates Board in respect of pantomographic examinations carried out on National Health Service patients.

The advantages of pantomographic radiology are that it provides an image of the entire dentition on a single film with all teeth visible from root to crown, it requires little expertise on the part of the dentist since the alignment of the X-ray tube and the film is automatic, and it takes only a minute or two to complete. In contrast, the most widely used conventional technique for acquiring similar diagnostic information involves taking between 11 and 14 intra-oral films each of which calls for accurate alignment by the dentist of the X-ray tube, patient and film. The inconvenience of the conventional technique limits its use in most dental surgeries to those cases where symptoms or visual inspection indicate possible pathology. Pantomography on the other hand is so simple that routine screening of asymptomatic patients presents no problems. In particular it facilitates regular checks on children to forestall problems associated with the replacement of the deciduous by the permanent teeth and potential malocclusions.

The possibility of patients acquiring significant lifetime doses from frequent routine radiographs started in early childhood, have prompted the NRPB to investigate the somatic doses associated with pantomographic and conventional dental radiography. Gonadal doses have not been considered since it has already been demonstrated (Jung, 1965) that they are exceedingly low (<0.0005 cGy)* for panoramic X-ray examinations of the teeth.

PREVIOUS STUDIES

Only three of the seven makes of pantomographic equipment known to be used by dental practitioners in this country have been studied previously with a view to assessing the radiological hazard to patients. All makes employ the same basic technique whereby the X-ray tube and the film cassette, which are horizontally opposed on either side of the patient's head, are made to rotate around the head in such a manner that a narrow beam of X rays simultaneously scans across the patient's teeth

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*Throughout this paper absorbed dose will be expressed in the SI unit centigray (cGy). This complies with the recommendations of the ICRP and BCRU and retains the same numerical values for this quantity as the old system of units, *i.e.* 1 cGy = 1 rad.

and the film. Technical details of this method are well documented in various publications (Manson-Hing, 1971; Van Aken, 1973; Updegrave, 1963). There are, however, differences in the beam geometry and the scanning motions used by the various manufacturers which may significantly affect the distribution of absorbed dose within the patient.

Kuba and Beck (1968) used ionization chambers and a Rando phantom* to determine doses at selected sites within the head and to the gonads from a Panorex set manufactured by S. S. White. The highest measured dose approached 0.6 cGy (0.6 rad) at the lateral centres of rotation. The skin below the ear lateral to the centres of rotation received the next highest dose, closely followed by the parotid gland. Howley and associates (Howley *et al.*, 1968) used lithium fluoride thermoluminescent dosemeters and a similar Rando phantom to determine both the radiation dose from a Panorex set and from a conventional full-mouth dental X-ray procedure using 14 films. They concluded that the patient radiation exposure is considerably less from the Panorex than from the conventional full-mouth series. Jerman *et al.* (1973) came to a similar conclusion after comparing the doses from a Panorex scan plus bitewing exposures against a full-mouth periapical series plus bitewing exposures, using calcium fluoride dosemeters on patients. Bushong *et al.* (1973) measured doses to the surface of a head phantom with lithium fluoride chips and concluded that the skin doses of between 0.2 cGy and 0.26 cGy to the lateral and posterior aspects of the head from a Panorex exposure were too high to justify large scale mass screening using this technique.

An attempt to compare the Panorex with the Orthopantomograph manufactured by Siemens and General Electric's Panelipse has been made by Manson-Hing and Greer (1977). They have published the exposures at 21 specific sites within the head and at the beam rotational centres following examination of a Rando phantom by each of the three machines. They summarize their findings by pointing out that exposures to internal sites vary from 0.3 mR to 2.4 R for the Panorex, from 0.4 mR to 0.8 R for the Orthopantomograph and from 0·2 mR to 1.4 R for the Panelipse, but leave it to the reader to decide which of these results is of least hazard to the patient. The Orthopantomograph has also been studied by Casebow (1973) and by Wohni (1977) who report highly localized doses of about 1 cGy and 0.7 cGy respectively at the lateral rotational axes for this equipment decreasing to about 0.12 cGy at the back of the head and to less than 0.02 cGy around the lips.

The reports discussed so far have all attempted to quantify the radiation exposure of the patient in terms of absorbed dose measurements at a few specific anatomical locations. Where the dose rate is changing rapidly over short distances and where the dose distributions in the head arising from different makes of equipment are not the same, such individual absorbed dose measurements are not very useful for comparison purposes. Suitable choice of measurement positions can make almost any technique appear favourable.

Nystron *et al.* (1975) have attempted to overcome this problem by measuring the total energy imparted to a phantom from a Siemens Orthopantomograph. This provides a single index of the exposure received by the patient that is likely to correlate more closely with the overall somatic hazard than a few individual dose measurements. They mapped the dose distribution with photographic film sandwiched between the transverse sections of a Rando phantom and summed the product of the mean dose and the mass of tissue, for volumes of tissue bounded by specific isodose curves. They arrived at a mean energy imparted of 4.5 mJ. Van Aken and Van der Linden (1966) attempted to calculate the same quantity by considering the energy flowing through a cross section of the X-ray beam before it enters the patient, both for the Siemens Orthopantomograph and for a conventional full-mouth series of intra-oral films. They neglected the loss of energy by transmission of the primary beam or scatter of secondary radiation out of the patient. Their value for the mean energy imparted by a Siemens Orthopantomograph was 1.1 mJ compared with 10 mJ for the conventional technique. The variation by a factor of four in the estimates by these two groups of workers of the energy imparted by an Orthopantomograph highlights the differences in their methods of calculating this quantity. Many sources of error exist in both methods. For example the doses measured by the photographic films of Nystrom *et al.* may well be larger than those occurring in practice due to the streaming of X rays down the gaps between the transverse sections of the phantom where the films were located.

Nevertheless, information on the energy imparted would provide a straightforward comparison of the relative somatic risk experienced by patients from these types of dental examination. If the same method for calculating this quantity is applied to all makes of panoramic equipment and to conventional techniques as well, any systematic errors inherent in the method should not invalidate the comparison.

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*The Rando standard man phantom is described in the following section on measurement techniques.

MEASUREMENT TECHNIQUES

The primary objectives of this study were to make consistent estimates of the energy imparted to the head and neck by pantomograms obtained with the equipment of all seven manufacturers known to have supplied the British market, and to compare these estimates with similar ones of the energy imparted by more conventional dental radiographic techniques. The degree of correlation between energy imparted and machine parameters like kV, mA and field size was to be investigated and measurement of the absorbed dose into organs suspected of having a high susceptibility to radiation-induced deleterious effects was considered to be desirable.

To meet these objectives 141 dosimeters were uniformly distributed throughout the head and neck of a Rando standard man phantom during simulated pantomographic and conventional examinations. By using such a large number of dosimeters a realistic value of the average dose to the head and neck could be derived irrespective of examination technique, and multiplication by the mass of tissue over which the dose had been averaged would yield the energy imparted.

Some of the dosimeters coincided with the location of the lobes of the thyroid and the eye lenses. Ten fell within the volume occupied by the parotid salivary glands. The susceptibility of these glands to radiocarcinogenesis is not well established but the work of Modan *et al.* (1974) suggests an excess incidence of parotid gland tumours following doses of a few cGy (rad) to the glands associated with the radiation treatment of ringworm of the scalp in children. Belsky *et al.* (1972) reported excess salivary gland tumours amongst Japanese atomic bomb survivors. The point is of particular interest in this study since the parotid glands lie close to the lateral centres of rotation of some of the pantomographic X-ray sets where the absorbed dose reaches a maximum value.

In the absence of reliable information on the distribution of active bone marrow within the skull and mandible it was assumed to be uniformly distributed, so that the average dose to the whole head would be a reasonable approximation to the average dose to the bone marrow within the head. The combined effect of the attenuation of X rays in the cortical bone surrounding the marrow cavities and the enhancement of the absorbed dose in the marrow due to secondary electrons arising from the adjacent bone, was taken to be negligible. In other words the dose to bone marrow could be equated to the dose received by adjacent soft tissue with insignificant error. The mean dose to the entire complement of active bone marrow within the whole body has been calculated by assuming that only the marrow within the head receives a significant dose and that the dose to the remainder is zero. Consequently, as 13.1% of the total active bone marrow in adults is thought to be located in the head (Ellis, 1961), the mean dose to the entire complement of bone marrow is assumed to be 13.1% of the average dose to the bone marrow within the head.

The dosimetry system consisted of suitably encapsulated lithium borate thermoluminescent powder whose performance and characteristics have been described elsewhere (Langmead and Wall, 1976). It has been specially developed at NRPB for medical dosimetry where its close tissue-equivalence and high precision enable doses down to 0.02 cGy to be measured with an overall uncertainty (random and systematic) of less than ±15%. The Rando phantom is made of a tissue-equivalent synthetic rubber and contains a human skull and mandible with a complete set of teeth, cervical vertebrae and airways corresponding to the maxillary sinuses, the buccal cavity and the trachea. It is divided into 25 mm thick transverse sections each containing a 3 × 3 cm matrix of holes for accommodating dosimeter capsules or tissue equivalent plugs. The dosimeter capsules are designed to hold about 35 mg of lithium borate powder at the centre of the transverse section. This keeps the sensitive volume of the dosimeter away from the gap between two sections where the radiation field might be perturbed by X rays passing along the gap with inadequate attenuation.

The pantomographic dental examinations were simulated on the phantom at various dental practices and hospitals throughout the North of England where equipment supplied by the seven manufacturers was in routine use. The values of tube voltage and current selected for these exposures were those that were necessary for obtaining good quality radiographs of the phantom.

The phantom was also exposed to conventional dental radiographic examinations at the University of Liverpool School of Dental Surgery. Two types of dental X-ray set frequently used by dentists in this country were chosen as representing the extremes of tube ratings commonly in use, namely 45 kV and 65 kV.

The Philips Oralix two-port set operated at 45 kV represents the older type of set with a relatively low output requiring a short focus-to-skin distance (FSD) of 10 cm. The larger of the two ports was used for our measurements and this gave a beam diameter at the cone tip of 5 cm. The smaller port is rarely used in practice because of the difficulty encountered in aligning the beam correctly.

More modern equipment is slowly replacing the older sets in dental surgeries, where operation at 65 kV provides a high output and allows for a longer FSD of 20 cm. A Philips Oralix 65 set was used to represent this later type of equipment, with a beam diameter of 6 cm at the cone tip.

Three types of conventional dental examination were simulated for comparison with the pantomographic techniques; the periapical full-mouth examination, bitewing views and oblique lateral jaw views.

The periapical view demonstrates the full length of teeth and the area associated with their roots, the bitewing view demonstrates the crowns of teeth especially the interproximal areas, and the oblique jaw view may be aligned to show the premolar and molar teeth of both the upper and lower jaws together.

For the full-mouth periapical examination a series of 11 dental films was used, this being the smallest number used in the various alternatives for this type of examination which provides similar diagnostic information to a single pantomograph.

For the bitewing examination two films were exposed on each side of the jaws. This is perhaps the most common type of dental radiographic examination for the detection of caries in the interproximal areas of the posterior teeth.

For the oblique jaw examination, one extra-oral film (size 18×13 cm) with a cassette fitted with fast tungstate intensifying screens was used on each side of the jaws. It is apparent that this examination provides about two thirds of the information obtained from a pantomograph. This examination was carried out on the 65 kV set only, as it was considered that the 45 kV rating was insufficient for this view.

Details of these techniques are described in the Kodak booklet *X-rays in Dentistry* and a list of the exposure factors used above is given in Table I.

Results and Discussion

Summaries of the data obtained are shown in Tables II and III for pantomographic and conventional dental radiography respectively. Up to ten repeats of each examination were simulated on the phantom to ensure that the doses actually received by the dosemeters were large enough to be measured accurately, but the values appearing in Tables II and III are those for a single examination only. The absorbed doses at ten anatomical locations are shown; these include the lens of the eye and the thyroid. Some indication of the dose distributions peculiar to each technique is thus given and comparisons can be made with previous reports which provide only discrete values of absorbed dose. Values for the mean dose to the parotid gland and to the entire red bone marrow and for the total energy imparted to the head and neck, appear at the bottom of each table.

The doses obtained with the Siemens Orthopantomograph appear to be in reasonable agreement with the values found by Casebow and Wohni but the first set of results shown for the S. S. White

TABLE I

Exposure factors used for conventional examinations

Examination	45 kV technique 5mA tube current 10 cm FSD	65 kV technique 7.5 mA tube current 20 cm FSD
	Exposure time (sec)	Exposure time* (sec)
Full-mouth periapical series		
Maxillary incisor region (2 films)	0.5	0.51
Maxillary pre-molar region (2 films)	0.6	0.59
Maxillary molar region (2 films)	0.7	0.88
Mandibular incisor region (1 film)	0.4	0.44
Mandibular pre-molar region (2 films)	0.5	0.44
Mandibular molar region (2 films)	0.6	0.51
Pre-molar and molar bitewings	0.8	0.51
Pre-molar and molar oblique view	—	0.29

*Times supplied by Philips, as not directly indicated on electronic timer.

TABLE II

ABSORBED DOSES AT SPECIFIC LOCATIONS, ORGAN DOSES AND THE ENERGY IMPARTED FOR EACH PANTOMOGRAPHIC TECHNIQUE INVESTIGATED

Location	Absorbed dose per examination, cGy (or rad)							
	Morita Panex E	S. S. White Panorex		G. E. Panelipse	Philips Ortho-Oralix	Fiad Rotograph	Siemens OPG	Sanko Panograph
Incisors	0.01	0.009	0.013	0.013	0.014	0.013	0.011	0.040
Centre of tongue	0.071	0.033	0.050	0.055	0.048	0.085	0.22	0.14
Pharynx	0.023	0.020	0.018	0.035	0.062	0.052	0.070	0.20
Corner of mouth	0.002	0.003	0.007	0.003	0.005	0.003	0.004	0.020
Centre of cheek	0.013	0.13	0.22	0.026	0.25	0.011	0.020	0.33
Below ear	0.074	0.13	0.16	0.10	0.18	0.20	0.20	0.37
Back of neck	0.047	0.002	0.006	0.094	0.077	0.14	0.12	0.19
Eye lens	0.001	0.001	0.002	0.008	0.003	0.002	0.002	0.010
Thyroid	<0.001	0.001	0.001	0.002	0.003	0.010	0.005	0.030
Parotid gland	0.045	0.077	0.087	0.056	0.12	0.13	0.12	0.28
Entire active bone marrow	0.002	0.002	0.004	0.003	0.004	0.005	0.005	0.017
Energy imparted to head and neck (mJ)	0.45	0.62	0.97	0.76	1.1	1.4	1.4	4.5

TABLE III

ABSORBED DOSE AT SPECIFIC LOCATIONS, ORGAN DOSES AND THE ENERGY IMPARTED FOR CONVENTIONAL TECHNIQUES AT 45 AND 65 kV

Location	Absorbed dose per examination, cGy (rad)				
	Full mouth series		2 left and 2 right bitewings		1 left and 1 right oblique
	45 kV	65 kV	45 kV	65 kV	65 kV
Incisors	0.29	0.13	0.10	0.10	0.020
Centre of tongue	0.12	0.29	0.040	0.10	0.010
Pharynx	0.036	0.050	0.020	0.030	—
Corner of mouth	1.0	1.2	0.65	0.33	0.005
Centre of cheek	0.59	0.46	0.22	0.37	0.12
Below ear	0.010	0.010	0.007	0.005	0.18
Back of neck	0.001	0.002	<0.001	<0.001	0.001
Eye lens	0.50	0.50	0.005	0.008	<0.001
Thyroid	0.001	0.002	0.002	0.002	<0.001
Parotid gland	0.012	0.033	0.006	0.013	0.073
Entire active bone marrow	0.11	0.017	0.004	0.006	0.002
Energy imparted to head and neck (mJ)	3.0	4.4	1.0	1.5	0.40

TABLE IV

FACTORS MOST LIKELY TO EFFECT THE ENERGY IMPARTED TO THE PHANTOM FROM THE SEVEN TYPES OF PANTOMOGRAPHIC EQUIPMENT INVESTIGATED

Equipment	Indicated kilovoltage (kV)	Indicated current × scan time (mAs)	Dimensions of beam at film cassette slit		Dose at film cassette slit for complete scan with no head in beam, cGy (or rad)
			Width (mm)	Height (mm)	
Morita, Panex E	81	123	8	180	1.1
S.S. White, Panorex	78	100	7	108	2.2
G.E., Panelipse	79	160	9	130	2.0
Philips, Ortho-Oralix	86	200	6	152	2.1
Fiad, Rotograph	79	216	6	168	2.4
Siemens, OPG	66	225	6	158	1.3
Sanko, Panograph	95	138	16	165	3.5

Panorex are generally lower than reported elsewhere (Kuba and Beck 1968; Howley *et al.*, 1968; Jerman *et al.*, 1973, Bushong *et al.*, 1973). This may well be due to the lower current of 5 mA considered adequate for good radiographs on present day machines in this country compared with the 10 mA used a few years ago in the United States. However, a second set of measurements was obtained on another Panorex machine installed in a different dental surgery using the same indicated voltage and current settings as before. Generally higher doses were obtained at most locations throughout the head in better agreement with other published data and leading to an increase in the energy imparted of 56%, compared with our measurements on the original machine. Appreciable variations in the dose delivered by nominally identical equipment are therefore to be expected and little significance should be attached to differences of less than 60% in the energies imparted by the various types of pantomographic equipment. This being the case, it can be seen from Table II that there is not much to choose between the middle five pantomographic techniques, but Morita's Panex E imparts about one half the energy and the Sanko Panograph at least three times the energy compared with the other five.

The factors most likely to affect the energy imparted are listed in Table IV. The dimensions of the X-ray beam in the plane of the slit immediately in front of the film cassette were measured with photographic film. The dose in the same position for a complete scan with an unobstructed beam was measured with lithium borate dosemeters to obtain relative values of X-ray tube output. The exceptionally large beam width used in the Sanko Panograph in conjunction with the higher kV and tube output would account for its higher values of energy imparted relative to the other sets tested. The low output of the Panex E is obviously responsible for its favourable dose characteristics but the reason for this low output could not be determined. Since the indicated kV and mAs values are no smaller than on other machines it seems likely that the Panex E incorporates more beam filtration than that used by other manufacturers. This was a factor that we were unable to check, since it would have required mechanical disturbance of the X-ray tube housing.

The doses measured at individual sites may vary between the different types of equipment because of differences in the scanning motion. For example the low dose seen at the back of the neck for the Panorex is to be expected because it has the unique feature of switching off the X-ray tube whilst it passes through a 20 deg arc centred posteriorly. Also the dose to the centre of the cheek depends critically on the proximity of the lateral axes of rotation. The Panex E and Panelipse use an eliptical scanning motion with no fixed centres of rotation and therefore show considerably lower cheek doses than the Ortho-Oralix or the Panorex where the lateral rotation centres lie close to the surface.

By comparing Tables II and III it can be seen that all pantomographic techniques except the Sanko Panograph impart less than half the energy to the phantom than the conventional full mouth periapical series conducted at 45 kV. When conducted at 65 kV the energy imparted by the periapical examination increases by 50%. Surface sites within the primary beam received similar doses from both periapical techniques but dosimeters located in deeper tissues and in tissues lying outside the beam were more heavily irradiated by the more penetrating radiation associated with the higher voltage technique.

An examination for interproximal caries involving two left and two right bitewing films can be seen to impart a similar amount of energy to the head as the majority of pantograms. Two oblique extra-oral films however impart only about a third of this energy.

Of the four organs selected as being of particular interest in somatic risk assessment, the thyroid and bone marrow can be seen to receive minimal doses (< 0.03 cGy) from all techniques. Doses to the lens of the eye are of significance only for the conventional periapical examinations and here they reach 0.5 cGy with both types of equipment. Even so, a patient would have to experience 3000 of these examinations before the threshold dose recognized by ICRP for the induction of cataracts large enough to impair vision was exceeded. The mean dose to the parotid salivary glands is higher for the pantomographic techniques than for the conventioanl periapical examinations and is in most cases due to its proximity to the lateral axes of rotation about which the X-ray beam rotates for part of the tomographic scan. Previous authors (Kuba and Beck 1968; Casebow 1973; Wohni 1977) have reported doses of up to, and possibly exceeding, 1 cGy at "hot spots" corresponding to these rotation centres but the biological significance of such highly localized doses is difficult to assess. By averaging the dose over the most highly affected organ (the parotid gland actually envelopes the hot spot for some pantomographic machines) the somatic consequences can be more easily appreciated. No technique delivers a mean dose of more than 0.28 cGy to the parotid gland and generally a dose of about 0.10 cGy is typical for pantomographic examinations.

Conclusions

The justification for medical diagnostic procedures involving the deliberate irradiation of patients lies in demonstrating that the diagnostic value of the radiographs outweighs any potential radiation hazard. In addition, in the situation discussed in this paper where a new technique becomes available which can, at least in part, replace older methods, it is necessary to establish that all essential diagnostic information is retained with the new technique at no increased risk to the patient.

Comparison of the total energy imparted to the head and neck during the various types of examination studied shows that the pantomographic technique usually produces less than half the energy imparted by the conventional 11 film, full-mouth periapical survey. It should be borne in mind however that whereas the value of the pantomographic technique is mainly confined to the routine general survey, the periapical intra-oral technique gives better diagnostic detail. A rational approach therefore would appear to indicate that a pantomographic survey could if necessary be followed up with two or three intra-oral views with less total exposure than the full-mouth periapical survey. For diagnostic purposes and radiographic observation during the period of development in children, pantomographic surveys are undoubtedly of value, but there is no necessity for repeating them more frequently than once a year between the ages of say eight to 16 years. Thereafter and throughout adult life there does not appear to be any clinical justification for making routine full-mouth radiographic examinations at intervals of less than three to five years, unless specific clinical conditions supervene. Thus in an average lifetime a patient should not be subjected to a total of more than about 20 pantomographic surveys.

The total energy imparted to the patient from this level of dental radiography amounts to some 20 mJ for a typical machine like the Philips Ortho-Oralix, and when compared to the 5 J that he is likely to receive from natural background radiation alone in the course of his life is seen to be relatively insignificant (0.4%). Even the most heavily irradiated organ, the parotid gland, will only receive about 2 cGy from 20 pantomograms, which represents about 30% of the mean dose that this organ will inevitably receive from natural background radiation during the same period. Consequently, if the frequency of pantomographic dental examinations is restricted in the manner outlined above, valuable diagnostic information can be obtained with very little increase in risk to the patient. Moving house to an area of lower natural background would be more effective in reducing the risk of radiation injury than further restricting dental radiographic procedures.

As regards bitewing examination of the interproximal areas, the survey indicates that the amount of energy imparted by the pantomographic technique is similar to that produced by taking four bitewing views. Bearing in mind the better visualization of interproximal caries that is usually obtained on the intra-oral bitewing film, it would seem reasonable to recommend that annual examinations of this type might continue to be justified despite the introduction of pantomography but that the number of films used should be kept as low as possible and in normal circumstances should not exceed four films per year. Such routine use of conventional dental radiography results in an upper limit of 1 mJ per year leading to possibly 50 mJ in a lifetime for the energy imparted, which may well exceed the contribution from pantomography although the dose to the parotid gland would be much lower.

Two oblique lateral jaw views (taken extra-orally) impart about one third of the energy of a pantomographic view. It has been suggested that one pair of oblique jaw views should provide about two thirds of the diagnostic information obtained from a pantomographic survey. There is therefore a firm implication that a reasonable full-mouth survey could be obtained by taking right and left oblique jaw views for the premolar and molar teeth and intra-oral views for the anterior teeth. This may be considered as an optimum procedure to obtain as much information as possible with a minimum of radiation exposure. Against this however would have to be balanced the standardization and ease with which a pantomographic view is taken and the frequency with which oblique jaw views may have to be repeated due to lack of expertise on the part of the operator.

In conclusion, the results of this survey indicate that the inclusion of pantomography in the equipment of the dental radiologist can provide useful diagnostic information with little or no increase in the risk of somatic injury to the patient, provided the technique is not used to excess. In particular, routine pantomographic surveys should be limited to a maximum of one per year during adolescence and one per three to five years during adulthood. All additional radiographic examinations should be individually justified. To ensure that the doses delivered do not exceed those quoted in this report, the X-ray equipment should be correctly installed, efficiently maintained, operators competently trained and recommended precautions for the reduction of radiation to the patient observed.

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Book review

Schädelhirnverletzungen im Computertomogramm. By W. Lanksch, Th. Grumme and E. Kazner, pp. x + 132 illus., 1978 (Springer Verlag K. G. Berlin) Price DM 68.00/ $34.00.

ISBN 3-540-08733-8.

Computed tomography in slightly more than five years has superseded the invasive radiodiagnostic techniques that gave neuroradiologists their reason to exist. This is true in all areas of intracranial diagnosis except subarachnoid haemorrhage, and none has benefited more from its introduction than the brain-injured patient. This short text, written by three practising neurosurgeons, is an analysis of clinical experience in two of the largest head-injury centres of the German Federal Republic. For the English reader, and even the neuroradiologist, this choice of authors for a book on computed tomography of the brain has its merits, which partly compensate for the inherent disadvantages of buying a German book, namely high cost, unfamiliar language and a list of references that is incomplete, not being oriented to the Anglo-Saxon literature. The chief merit of the book is the authors' clinical approach to their subject: throughout, the computed-tomographic appearances of head injuries are discussed in the light of what the neurosurgeon can obtain from the method for his patient, in diagnosis, continuing management and prognosis. This book is not an exercise in pattern recognition—and therefore a refreshing change from the recent spate of trans-Atlantic computed tomographic texts—it is a monograph, because it could be a basis for the head-injury chapter of a textbook of neuroradiology. The text, supplemented by the 141 illustrations, deals comprehensively with the majority of commonly-encountered computed-tomographic patterns of the injured brain. The statement is made that the picture of traumatic ventricular displacement without variation in parenchymal density is almost always due to an isodense subdural haematoma, and much of the discussion concerned with interpretative error centres upon this entity. The authors observe that a small but significant proportion of their patients with severe closed head injuries showed no abnormality on computed tomography. However, writing as practising neurosurgeons, they claim that there are probably only two residual indications for carotid angiography in head-injured patients, viz. to elucidate the isodense mass of computed tomography, and to diagnose brain death.

E. H. Burrows.

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Radiation dose to the fetus in obstetric radiography

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ABSTRACT

The mean dose to the fetus and fetal head, together with the doses to the fetal gonads and maternal gonads, have been estimated to be 107, 56, 131 and 136 mrad respectively for an obstetric prone oblique examination of the abdomen, using a rare-earth screen-film combination. The doses were derived by measuring skin doses on a series of women in late pregnancy undergoing the above examination and by using measured depth-dose information. The position of the fetus relative to the maternal skin surface was determined by ultrasonic scanning.

The minimization of dose received by patients in obstetric radiography is particularly important because it is believed that the fetus may be up to ten times more sensitive than the adult to the production of radiation-induced leukaemias (ICRP, 1966). There have also been several reports demonstrating that children exposed to X rays *in utero* have an increased risk of dying from cancer (Bithell and Stewart, 1975; MacMahon, 1962) although others have failed to show such an effect (Court Brown *et al.*, 1960). In any case, it is generally acknowledged that there is an increased cancer risk associated with ante-natal radiography, although the magnitude of the risk is still uncertain and may partly be due to other factors (UNSCEAR 1972b).

In addition to the carcinogenic effect of radiation there is also the risk of genetic damage. In obstetric radiography both the mother's gonads and those of the fetus are irradiated, resulting in a relatively high contribution to the total genetically significant dose (GSD) from diagnostic radiology. At the time of the Adrian survey (Adrian Committee, 1960) the obstetric abdomen examination contributed 26% to the GSD, although the later Sheffield survey (Matthews and Miller, 1969, UNSCEAR, 1972a) indicated that this figure had been reduced to 11%. Although difficult to quantify, various attempts at estimating the risks of genetic damage have been made, for example by the Advisory Committee on the Biological Effects of Ionizing Radiation (BEIR, 1972).

While it is of course, a general principle that the radiation dose to the patient should be kept to the minimum consistent with clinical needs, a reduction in dose in obstetric radiography could be particularly advantageous for the reasons outlined above. The introduction in recent years of rare-earth phosphors in the manufacture of intensifying screens has enabled doses in general radiography to be reduced by factors of two to four without loss of image quality (Pritchard and Hufton, 1976; Soila *et al.*, 1977; Ardran *et al.*, 1976). The doses in fetal radiography using a rare-earth screen-film combination have therefore been derived and the results are presented here.

MATERIALS AND METHODS

The examination considered is the prone oblique abdomen as described by Russell (1973) and the work was carried out in the Department of Radiology, St. Mary's Hospital for Women and Children, Manchester.

Radiographs were taken with a Machlett Dynamax HD50B high-speed anode X-ray tube and a GEC Watson Roentgen 8 three-phase generator. The total tube filtration was stated to be 2.7 mm Al equivalent and the kV as measured by the Ardran-Crooks penetrameter was within 2 kV of the dial setting, in the kV range used. Typical exposure factors ranged from 52 kV, 110 mAs to 60 kV, 150 mAs, the average being 56 kV, 141 mAs. A focus-film distance of 100 cm was used together with compression of the patient and an 8 to 1 ratio Potter-Bucky grid. The Ilford Rapid R films, exposed between a pair of Ilford Rapide rare-earth screens, were processed in a Pako $3\frac{1}{2}$ minute automatic processor.

Skin doses received by 75 patients were measured by thermoluminescent dosimetry, a small plastic sachet containing 30 mg of lithium fluoride being placed on the skin surface at the centre of the X-ray field. The calibration of the lithium fluoride was performed by comparison with a 35 cm^3 ionization chamber and EIL electrometer, the calibration of which was traceable to the National Physical Laboratory. Also recorded for each patient were the exposure factors used, and the focus-skin distance both before and after the application of compression.

Initially it was planned to scan each patient with ultrasound at the time of her X-ray examination in order to determine the position of the fetus in relation to the maternal skin surface. However, this proved to be impractical and instead scans were performed on a small sample of patients. Although difficulty was experienced in obtaining meaningful displays with the patient in the prone oblique position, ultrasonic B scans of transverse and longitudinal sections through the fetus were taken enabling average depths and shapes of the fetus to be determined for use in the dose calculations.

Depth dose curves were obtained for various kilovoltages by using a 35 cm^3 ion chamber to measure the dose at various depths in a 15×15 cm hardboard phantom. Tests on a different X-ray set, using a water phantom in addition to the hardboard phantom, indicated that, for a given dose, the depths in hardboard needed to be reduced by 10% to obtain equivalent depths in water. Subsequently a disc-shaped ionization chamber 0.5 cm thick became available and it was possible to check the perturbation effect of the 35 cm^3 chamber (diameter 3.6 cm) by comparing depth dose curves measured using each chamber. It was found that at the depths of interest here, that is greater than 6 cm, no corrections were necessary. The depth dose curves beyond 2 cm deep were found to be simple exponentials. These data were then stored on a computer together with the results of the ultrasonic scans and the exposure factors, skin doses and focus-skin distances used for each patient. The above information enabled an average dose to the fetus to be derived for each patient by calculating the dose at points 1 cm apart in a 3 dimensional grid within the volume occupied by the fetus. Samples of the radiographs taken showed that on average 43% of the fetus was shielded by maternal spine and pelvis and in the vertex presentation the fetal head was completely shielded.

It was assumed that the average thickness of bone shielding the fetus was 0.5 cm, and since the mass attenuation coefficients of bone and aluminium are very similar, this thickness is equivalent to 0.35 cm of aluminium allowing for the difference in density. An estimate of the effect of the bone shielding was thus obtained by measuring the reduction in dose at a depth in a phantom when 0.35 cm of aluminium was placed on the surface of the phantom. This indicated that the average dose to the fetus was reduced by approximately 15% and the dose to the head by 35% due to the shielding effect of the maternal spine and pelvis. In calculating the gonad dose it was assumed that the fetal gonads were at a depth in the fetus equal to half the fetal thickness. Similarly it was assumed that the maternal ovaries were at a level just above the iliac crests and at an average depth equal to half the maternal thickness. In fact, because of the oblique position one ovary will be slightly nearer the X-ray tube than the other and both may be partially protected by the pelvis in some patients (Hibbard, 1961).

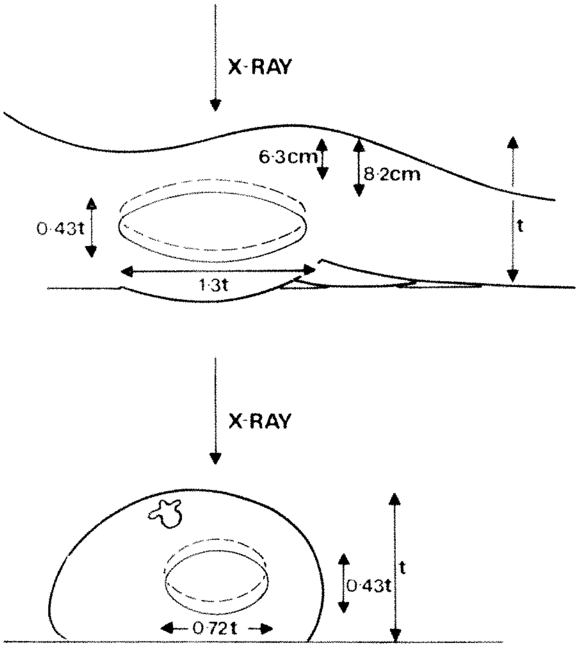

FIG. 1.

Position of mother and assumed position of fetus during X-ray examination. Dashed line is assumed position of fetus for anterior placental sites. Solid line is assumed position of fetus for posterior placental sites.

RESULTS

From the ultrasonic measurements no correlation was found between the depth of the fetus below the skin surface and any easily measurable parameter such as fetal maturity or thickness of patient. As might have been expected, however, a significant difference was found between patients with anterior placentas and those with posterior placentas. The best estimate of the depth of the fetus was found to be 6.3 cm for anterior placental sites and 8.2 cm for posterior placental sites. These depths are the distances between the point on the skin surface at the centre of the X-ray field and the nearest part of the fetus. To simplify the calculations it was also assumed that the fetus was ellipsoidal in shape with vertical axis equal to $0.43t$, transverse axis $0.72t$, and longitudinal axis $1.3t$, where t was the compressed thickness of the mother. This information is depicted in Fig. 1 which shows the positions of the patient and fetus during the X-ray examination. The ultrasonic scans showed these to be reasonable assumptions. Out of the total of 75 patients 31 had anterior placental sites, 28 posterior placental sites and the sites of the remainder were not recorded. The average thickness of the patients was 25 cm without compression and 21 cm with compression applied, and the

TABLE I

RESULTS OF DOSE DETERMINATIONS

	Absorbed dose (mrad)	
	Mean	Standard deviation of individual doses
All placental sites		
Average fetal dose	107	41
Average dose to fetal head	56	21
Fetal gonad dose	131	41
Anterior placental site		
Average fetal dose	130	41
Average dose to fetal head	68	21
Fetal gonad dose	157	37
Posterior placental site		
Average fetal dose	78	16
Average dose to fetal head	41	8
Fetal gonad dose	99	7
Maternal skin dose	1500	500
Maternal gonad dose	136	29
Integral dose to fetus (all placental sites)	247 g.rad	216 g.rad

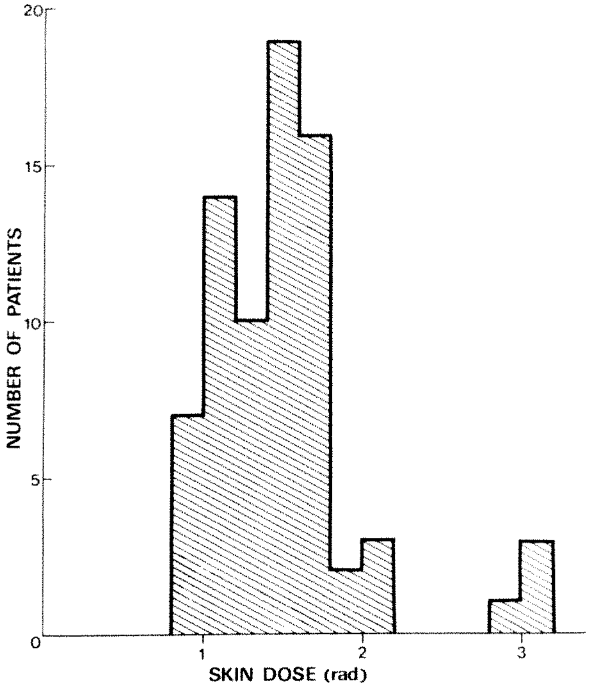

FIG. 2.
Maternal skin dose distribution.

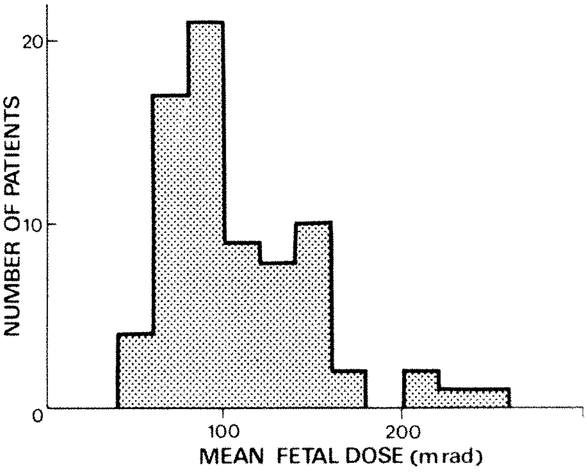

FIG. 3A.
Mean fetal dose distribution.

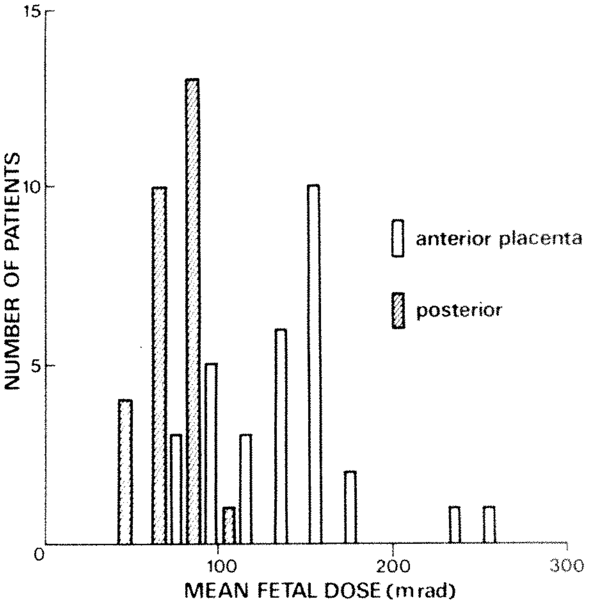

FIG. 3B.
Mean fetal dose distribution for anterior and posterior placental sites separately.

average bone age of the radiographed fetuses was 36½ weeks.

The doses determined are given in Table I and the distribution of maternal skin doses and average fetal doses are shown in Figs. 2 and 3. For those patients whose placental sites were not recorded the fetal doses were calculated assuming that the fetus lay mid-way between the positions for anterior and posterior placental sites, *i.e.* at a depth of 7.2 cm. The variation in the measured skin doses is due mainly to the differences in size of the patients and the consequent variation in the exposure factors necessary. Although this is part of the cause of the variation in average fetal dose, an additional factor is variation in the distance between the fetus and the film. If this distance is known more precisely, for example if it is known that the placenta was sited anteriorly, then the standard deviation is smaller than if the placental site was unknown, in which case the fetus may have occupied a wider range of positions. The difference in fetal doses for the different placental sites is due to the different assumed depths of the fetus. However, the spread in both skin doses and fetal doses is significantly smaller for patients with posterior placental sites. It is perhaps worth noting that because the overall fetal dose distribution is not symmetrical about the mean, the most probable dose is not equal to the average dose. Thus if one wanted to know the dose given to an individual fetus, *i.e.* the most probable dose, this would be 77 mrad, whereas the average of many fetal doses is 107 mrad. This is partly due to the combination of the two distributions, each having different means and standard deviations, for the different placental sites.

The variations in observed skin doses and calculated fetal doses are much larger than the errors associated with their determination, within the assumptions made. For example the random error associated with the individual dose measurements is about ±5% while that due to rounding off errors in the computer program is about ±1%. The largest errors are connected with the assumptions made, namely the depth and thickness of the fetus, and variations in tissue composition and density, which were only approximately allowed for in the bone-shielding correction. At 56 kV the measured half value thickness is 2.8 cm of water so variations in overlying maternal tissue can affect the dose to the fetus considerably.

DISCUSSION

As indicated in the introduction, there is evidence that even the low levels of radiation prevailing in ante-natal radiography may sometimes have a carcinogenic effect. About half the increased risk is that of leukaemia induction (UNSCEAR 1972b) and it has been suggested that the average dose to the fetus is the best estimate of the mean bone-marrow dose (Adrian Committee, 1966) and hence the important physical parameter in considering the leukaemia risk. It has been noted, however, that most of the extra leukaemias are non-myeloid, and therefore it is not known what proportion of them can be attributed to irradiation of the bone marrow and what proportion can be attributed to irradiation of other organs (ICRP, 1969). In view of these difficulties and to simplify the calculations the fetal dose given here assumes the whole fetus to be tissue-equivalent. The dose to the fetal head has also been determined, not only because it is rather lower than the dose to the rest of the fetus due to the shielding effect of the mother's pelvis, but also because it may be of importance in connection with tumours of the central nervous system which are the most common solid tumours in childhood. In fact, the dose throughout the fetus is far from uniform in which case it may be noted that the usefulness of an integral dose, or average dose, presupposes a linear relationship between dose and probability of effect (Mayneord and Clarke, 1975).

Such a linear relationship has been shown by Stewart and Kneale (1970) to describe adequately the data from the Oxford Survey of Childhood Cancers (OSCC). Using these data and the assumption of linearity, together with revised estimates for the fetal doses, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1972b) have estimated that 23 extra deaths per million exposed fetuses per year per rad over a 10 year period are associated with antenatal radiography. Thus a fetal dose of 107 mrad, as determined by this study, would lead to an extra 25 deaths over ten years for every million radiographs taken, or, in other words, the fetus would run an excess risk of about 4% of dying from cancer in the first ten years of its life. However, it should be pointed out that the possible errors in these figures are very large, and moreover the Oxford data can equally well be described by, for example, a dose squared relationship which would result in relatively much smaller risks from small doses, as shown in the analysis presented in the Appendix. Hence it would appear that it is not possible at the present time to estimate reliably the excess cancer risk due to ante-natal radiography.

Average doses from a variety of techniques and departments have been derived in the national survey (Adrian Committee, 1960, 1966). In this the mean fetal bone-marrow dose was found to be 500 mrad, the dose to the fetal gonads 723 mrad and the maternal gonad dose 367 mrad, while the smaller survey of Matthews and Miller (1969) found figures of 230 mrad for the maternal gonad dose and 203 mrad for the fetal gonad dose.

The dose to the fetus can be minimized by ensuring that it is as near to the film cassette as possible: hence the use of the PA projection as opposed to the AP. Compression will also help in this matter and will, moreover, reduce movement blurring and scatter. The contrast and speed of several film–screen combinations have previously been investigated and the image quality assessed subjectively (Pritchard and Hufton, 1976). The fastest film–screen combination was then chosen which satisfactorily depicted the fetal epiphyseal centres, essential for assessing fetal maturity. These centres are initially of low inherent contrast and their visualization probably depends primarily on the noise properties, as opposed to resolution properties, of the film–screen combination used. A low kV technique is used to maximize contrast. Raising the kV would reduce the fetal dose but at the cost of lower contrast and increased quantum mottle. It is clear that further investigations are needed in this branch of radiology to quantify the image quality with different screens and films and its variation with such parameters as kV, scatter–grid properties and dose to the patient. Since the assessment of diagnostic quality depends also on the anatomical details considered to be of importance, and on the observer – *i.e.* the radiologist, any meaningful investigation will have to take these factors into account.

SUMMARY AND CONCLUSION

An average fetal dose of 107 mrad has been determined for obstetric abdomen radiography using a low kV technique and a rare-earth screen–film combination. Although obtained in a single department and using a constant technique this figure is subject to large individual variations, due mainly to differences in sizes of patients and in the size and position of the fetus. This dose is about five times lower than the average found by the Adrian survey (Adrian Committee, 1966) and the corresponding gonad doses are about half those found in the later survey of Matthews and Miller (1969). It does not seem possible at present to attach a reliable estimate to the increased cancer risk due to this whole body irradiation of the fetus. Finally, a quantitative assessment of image quality is needed as a basis for determining the acceptability of the consequences of further reductions in dose.

ACKNOWLEDGMENTS

The work was carried out in the Department of Radiology, St. Mary's Hospital for Women and Children, Manchester and thanks are due to the Consultant Radiologist, Dr. J. G. B. Russell, for suggesting the work and providing assistance and information throughout.

APPENDIX

Stewart and Kneale (1970) have shown that the data from the OSCC can be described adequately by a linear dose response relationship. Although it was realized that there would be some error in the estimated doses per film (Bithell and Stewart, 1975), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1972b) estimated the fetal doses prior to 1960 to be rather higher than those assumed by Stewart and Kneale (1970).

An analysis is presented here in which both linear and quadratic forms of dose-response relationship are fitted to the OSCC data. The main conclusions are that linear and quadratic relationships fit the data equally well, using either the original dose estimates (Stewart and Kneale, 1970) or those estimated by UNSCEAR (1972b).

Figure 4 shows the incidence of cancer, relative to the normal incidence, versus fetal dose from the data of Stewart and Kneale (1970), but using the doses per film given by UNSCEAR (1972b). The vertical error bars shown are standard deviations, assuming the number of children in each dose category follow a Poisson distribution. The calculation of the standard deviation is complicated by the fact that the numbers in each of the four categories – i.e. cases X-rayed, cases not X-rayed, controls X-rayed and controls not X-rayed – are not independent. Nevertheless, the error on a particular point will largely be determined by the smallest of the four numbers. As can be seen from Fig. 4, individual data points have been used since any combination of points will result in a loss of information, the resulting averages obviously depending on how the individual points are grouped.

A linear relationship of the form $y = a + bx$ and a quadratic of the form $y = a' + b'x^2$ were fitted to the data by minimizing the expression

$$\chi^2 = \Sigma_i \left(\frac{y_i^{o} - y_i^{c}}{\sigma_i}\right)^2$$

The y_i^{o} are the observed relative cancer incidences and the y_i^{c} those calculated according to the assumed relationship. The σ_i are the standard deviations on the y_i and x represents the fetal dose in mrad. The fitted parameters are given in Table II together with their standard deviations. The inclusion of a and a' is to allow for the fact that there may be an excess risk over the normal incidence of cancer even if no

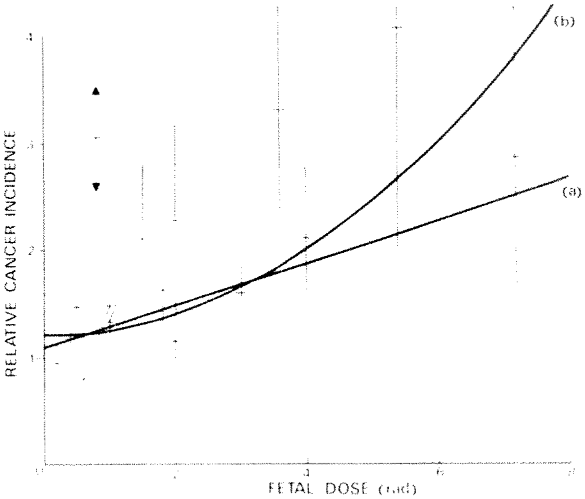

FIG. 4.

Incidence of cancer, relative to the normal incidence, versus fetal dose from the data of Stewart and Kneale (1970), assuming UNSCEAR (1972b) doses. Curve (a) $y = 1.09 + 0.195x$; Curve (b) $y = 1.20 + 0.049x^2$. The error bars on the dashed point at 800 mrad have not been drawn in full due to the large standard deviation of 3.5.

TABLE II

Details of linear and quadratic fits to the OSCC data

	a	σa	b	σb	χ^{2}*
Original dose estimates					
Linear: $y = a + bx$	1.08	0.15	4.62×10^{-4}mrad^{-1}	2.71×10^{-4}mrad^{-1}	13.5
Quadratic: $y = a' + b' x^{2}$	1.19	0.11	3.33×10^{-7}mrad^{-2}	1.81×10^{-7}mrad^{-2}	13.1
Revised dose estimates					
Linear: $y = a + bx$	1.09	0.14	1.95×10^{-4}mrad^{-1}	0.91×10^{-4}mrad^{-1}	11.9
Quadratic: $y = a' + b' x^{2}$	1.20	0.10	4.90×10^{-8}mrad^{-2}	2.21×10^{-8}mrad^{-2}	11.5

* Number of degrees of freedom = 14.

radiographs are taken. This is because some of the factors which lead to the selection of women for obstetric radiography are themselves associated with a higher than normal incidence of cancer in the children of these women (Russell, 1973).

All the fits are acceptable, the chi-squareds for the data using the UNSCEAR doses being slightly lower than those for the data using the original dose estimates, and the chi-squareds for the quadratic fits being lower than those for the linear ones. At zero dose the linear relationship predicts an excess risk over the normal incidence of about 9% and the quadratic an excess of about 20% although both these figures have large associated errors. If one compares the relative cancer incidence at a given dose with that at zero dose, in order to obtain the risk due to the X-rays, it can be shown that the quadratic relationship gives a much lower excess risk than the linear at the dose levels now prevailing in obstetric radiography. For example, for an average fetal dose of 107 mrad, as derived in this study, substitution into the equations given in Table II shows that the quadratic fit predicts an X-ray induced excess risk some 40 times less than that predicted by the linear fit: *i.e.* 0.05% as compared with 2%. Since the parameters of the two fits are not accurately determined there will be substantial errors associated with these figures. Furthermore, only two simple forms for the dose-response relationship have been investigated, and it is quite possible that the data can be fitted equally well by other curves. However, this does illustrate the caution needed when deriving risk factors from data which are not able to distinguish between several different forms of dose-response relationship. It is obviously not sufficient to show that the data are compatible with a particular form of dose-response relationship, on the basis of say the χ^{2}. The significance of different forms of dose-response relationship are discussed in more detail by, for example, Mole (1975) and Mayneord and Clarke (1975).

The relative cancer incidence can be converted to an actual death rate by assuming a natural cancer incidence of about 700 deaths per million live births over a ten year period (Stewart and Kneale, 1970). This gives a figure of 136 deaths per million exposed persons per rad ($136/10^{6}$/rad) derived from the linear relationship using the OSCC data with the UNSCEAR doses, which is somewhat lower than the UNSCEAR figure of $230/10^{6}$/rad derived from the same data (UNSCEAR, 1972b).

In summary, it is seen that the existing data on cancer deaths following ante-natal radiography do not permit distinction between an excess cancer risk which is proportional to dose and one which is proportional to dose squared over the dose range 0.2-8 rad. Apart from other difficulties, it would seem that the relatively small numbers involved in available data and the large uncertainties in fetal doses prevent a reliable estimate being made at present of the relationship between excess cancer deaths and fetal absorbed dose.

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Lung damage in C57Bl mice following thoracic irradiation: enhancement by chemotherapy

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ABSTRACT

C57Bl mice were treated with thoracic irradiation to doses in the range 12.0 to 18.9 gray. Few deaths were observed in the period 80–160 days after irradiation (an end-point of lung damage used by other investigators) and the median survival times ranged from 200 to 310 days. CBA mice treated under identical conditions predominantly died between 80–160 days and it is therefore concluded that C57Bl mice show unusually prolonged survival following this treatment. Six chemotherapeutic agents were given to C57Bl mice together with thoracic irradiation, in most cases two weeks beforehand. Adriamycin, bleomycin and cyclophosphamide enhanced the mortality of the mice. Most agents had little effect on radiation-induced skin damage.

The increasing tendency for chemotherapy to be given in conjunction with radiotherapy requires clinical decisions on whether this will lead to an increase in normal tissue damage and whether, and to what extent, radiation dose should therefore be reduced. To fail to reduce the dose in the presence of considerable enhancement could lead to over-treatment; to reduce the dose unnecessarily could negate the benefit of adding chemotherapy. The investigations described here were planned as an extension of the work of Phillips and co-workers (Phillips *et al.*, 1975; Phillips and Fu, 1976) who have determined dose enhancement factors for various chemotherapeutic agents and a number of end-points involving normal tissue damage. Since in this laboratory we are making extensive use of the Lewis lung tumour and B16 melanoma growing in C57Bl mice, it was decided to use this strain for the studies of normal tissue damage also. The main objective of the experiments was to use mortality after thoracic irradiation as an endpoint for lung damage, but as a by-product some skin reaction data were also obtained.

MATERIALS AND METHODS

Minimal-disease male C57Bl mice were obtained from the Institute of Cancer Research breeding station. They were kept in a conventional animal house, fed on autoclaved diet (Spratts lab diet no. 1) and given water *ad libitum.* After irradiation, each batch of mice was ear-marked and the mice within an experiment were uniformly mixed among the cages. One experiment on CBA mice produced in the same breeding laboratory and maintained under identical conditions is also described.

Irradiations were performed in a circular plastic chamber using an X-ray machine operating at 230 kV, 15 mA, filtered with 1 mm Cu and 1 mm Al. The chamber was designed to hold ten 25 g mice. For each experiment, mice weighing 24–26 g were selected on the day before irradiation or on the day before chemotherapy. Although chemotherapy was often given two weeks before irradiation it was reasoned that growth during this period would largely be off-set by weight loss due to the administration of drugs. The Perspex chamber measured 36 cm in diameter, 2 cm deep, with a ring of Perspex pegs at a radius of 5.5 cm (Fig. 1). These pegs were in pairs with a 9 mm gap (13.5 mm between centres), a dimension that was found to locate securely the neck of a 25 g mouse without constricting the throat. Blocks of expanded polystyrene located the abdomen of each mouse. The circular lid of the chamber was made of 2.5 mm Perspex, on the top of which was bonded a sheet of 3 mm lead. The depth of the chamber was such that the Perspex lid was in contact with the back of each mouse. Air was passed into the chamber through a radial tube leading to the central boss. A diaphragm pump produced a flow-rate of about 1.6 litre/min and the air stream was passed through a copper coil immersed in a water-bath at 32°C before entering the chamber. The chamber was supported on a 3 mm sheet of aluminium (as a heat-spreader) which rested on a thick rubber mat over a gentle warming plate, and before a series of irradiations the air stream was switched on and the chamber pre-warmed. A paramagnetic oxygen analyser connected to the outlet from the chamber allowed the oxygen concentration to be checked and it was found that when the chamber contained ten mice and air was passed at 1.6 litre/min the oxygen concentration was indistinguishable from that of air.

For irradiation, the chamber was located centrally underneath the X-ray machine with the top of the

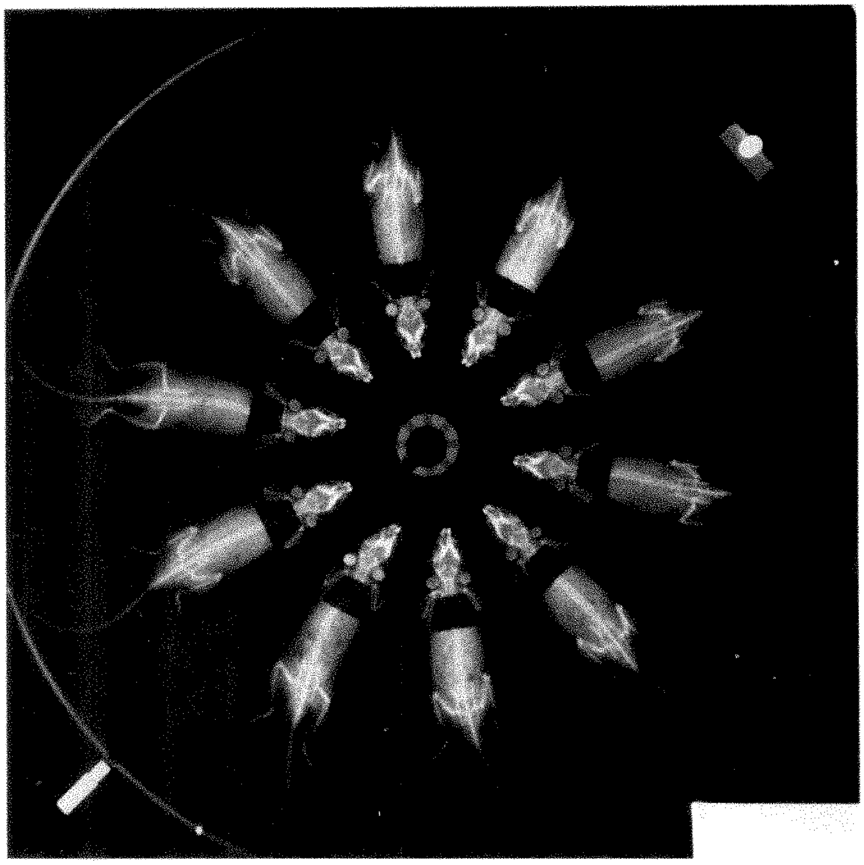

Fig. 1.

Double-exposure radiograph of mice within the irradiation chamber. Exposures were made with and without the "small field" lead shield. In order to produce this radiograph it was necessary to use a focal distance of 100 cm (almost three times that used for irradiations). There is therefore a parallax error in this radiograph which makes the fields appear to be 3 mm closer to the head of the mouse, in real terms.

lid at 37 cm from the target. This was facilitated by bolting to the exit port of the X-ray head an aluminium ring carrying three parallel legs. Three circles were marked on the lid of the chamber, with which the legs were located. Two lids were available, in each of which the lead sheet overlying the chamber had ten trapezoidal holes cut out. For "small field" irradiation, the fields had a width that tapered from 19 to 12.5 mm with a depth of 13.5 mm. For "large field" irradiation the width tapered from 21 to 12.5 mm with a depth of 16.5 mm. The two fields thus differed in that the lower (thoraco-abdominal) boundary was 3 mm deeper for large field irradiations. X-ray films taken with the therapy set and diagnostic films were used to check that the fields were centrally placed over each mouse position and coincided at the anterior border with the upper limit of the rib-cage.

Groups of ten mice were anaesthetised with sodium pentobarbitone, placed in the chamber as soon as they would lie still, and irradiated. The irradiations took up to about 18 min at a dose-rate of approximately 1.2 Gy/min. The dose-rate was measured with a Baldwin-Farmer dosemeter. The lid of the mouse chamber was removed and the ionization chamber was placed in the position of the thorax of one mouse. To eliminate scatter, lead sheets were placed so as to expose the full volume of the detector but defining an area not much greater than one of the lung fields. Readings were corrected for pressure and temperature, and a rad-roentgen correction of 0.96 was assumed for lung tissue.

The irradiated mice lost hair and often developed a skin reaction over the dorsal thorax that corresponded to the trapezoidal radiation field. The extent of this reaction was scored approximately twice weekly using a simple arbitrary scale as described by Field (1969) and Steel *et al.* (1978).

RESULTS

Choice of field-size

Since the posterior border of the lung lines the diaphragm which is inclined between the dorsal and ventral surfaces, it is impossible with a vertical field to irradiate all of the lung and none of the liver or stomach. The positioning of the lower boundary of the thoracic field must therefore depend upon whether it is preferable to miss a small amount of lung or to irradiate other organs.

The "small" lung fields were designed to avoid irradiating much of the liver, whilst missing a certain amount of lung tissue. Evidence for this came from an ancillary experiment in which the eradication of artificial lung metastases was investigated. Mice were given intravenous injections of a suspension of Lewis lung tumour cells, with added microspheres and heavily-irradiated cells (Steel and Adams, 1975). Starting on day 1 after this procedure and at intervals thereafter, groups of ten mice were given thoracic irradiation using "small" lung fields to a dose of 17.2 Gy. The mice were then observed for 80 days. Unirradiated mice all died within 24 days with an average survival time of 20 days. Their lungs were excised and found to contain an average of 11 colonies countable on the lung surface (Steel and Adams, 1975). Seven out of ten of the mice irradiated on day 1 survived to 80 days. When the irradiation was delayed for ten days after the implantation of cells the survival fell to zero. However, half of the mice irradiated on days 1 and 3 were found to have tumours confined to the lower poles of the lungs. This was taken to be evidence that some lung tissue that had taken up tumour cells had been missed by the "small" radiation fields.

The experiment was repeated using "large" lung fields and the results are shown in Fig. 2. In this experiment the unirradiated mice developed an average of 17 lung colonies. It can be seen that mice irradiated on days 1, 3 or 6 were all cured by thoracic irradiation, indicating that the "large" lung field irradiation gave complete coverage of lung tissue. These results also show that intravenously-injected Lewis lung cells were confined to the lung for six days after injection, an interesting finding that confirms the work of Proctor *et al.* (1976). The deaths of animals irradiated at later intervals were attributed to metastatic spread from lung as well as to failure to control the lung tumours themselves. On the basis of our earlier studies on the growth and radiosensitivity of pulmonary colonies of Lewis lung tumour (Shipley *et al.*, 1975; Steel *et al.*, 1976) we estimate that a single dose of 20 Gy would fail to cure animals bearing an average of 17 colonies per lung at about day 11.

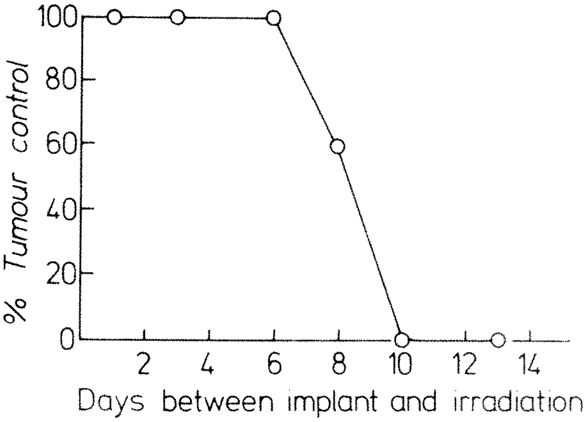

FIG. 2.

Proportion of mice given an intravenous injection of Lewis lung tumour cells that were cured by thoracic irradiation given at the times indicated. The dose was 17.2 Gy using the "large" lung field.

Effect of field-size on mortality

Groups of ten mice were given thoracic irradiation using the "large" or "small" lung fields. No animals died in this experiment before 100 days and only two died within the period 80–160 days that has been used by Phillips and others as the end-point for lung mortality (Phillips *et al.*, 1975; Field *et al.*, 1976). The median survival times are plotted in Fig. 3 and they ranged from 200–300 days. Mice irradiated with the "small" lung fields survived up to 30 days longer than those with the "large" lung fields, but this was not felt to be an important difference. Animals that survived an injection of Lewis lung tumour cells when given 17.2 Gy thoracic irradiation up to six days later (see previous section) survived for a similar time to non-tumour bearing animals. The lowest open triangle in Fig. 3 was for the group irradiated one day after the injection of cells. Their post-irradiation survival time may have been slightly shortened by the implantation procedure.

The pathology of the animals at the time of death was examined by Professor S. L. Kauffman. Shortly before death the mice showed signs of respiratory difficulty. Histological examination of the lungs showed zones of pulmonary oedema. Inflammatory cells were seen within the capillaries, around some terminal bronchioles, and in the connective tissue around bronchial arteries. There were large numbers of macrophages and some pulmonary haemorrhage. This picture was consistent with the observations of Phillips and Margolis (1972) and with a diagnosis of acute bronchopneumonia.

Effect of chemotherapeutic treatment on radiation-induced lung damage

Six chemotherapeutic agents were chosen for this investigation (Table I). Maximum-tolerated single doses were used, and all except cyclophosphamide were given 13 or 14 days before thoracic irradiation. The clearance of these drugs from the circulation is largely complete within 24 hours of administration. Two different dose levels for bleomycin and adriamycin were used because of uncertainties in the tolerance doses. Cyclophosphamide was given either three hours before or two hours after radiation, for comparability with our earlier study (Steel *et al.*, 1978). Although the metabolism of cyclophosphamide is rapid, there may have been some residual cytotoxic metabolite present at two hours after injection. All the mice that received drugs plus thoracic irradiation were given a radiation dose of 15.5 Gy using the "small" field.

The pattern of mortality of the mice given combined treatment is shown as Fig. 4. There was

TABLE I

Doses of cytotoxic agents and skin reaction results

Drug	Timing in relation to irradiation (days)	Dose (mg/kg)*	Average Skin reaction**
Methotrexate	−13	150.0	1.12
Vinblastine	−13	2.0	1.05
Actinomycin	−13	0.75	0.90
Bleomycin	−13	100.0	1.29
	−14	75.0	1.51
Adriamycin	−14	7.5	1.04
	−14	10.0	0.95
Cyclophosphamide	− 3 hours	200.0	1.25
	+ 2 hours	200.0	1.20
Controls (2 experiments)			1.12 1.27

* All drugs given by i.p. injection.
** Averaged over the period 20–60 days after irradiation.

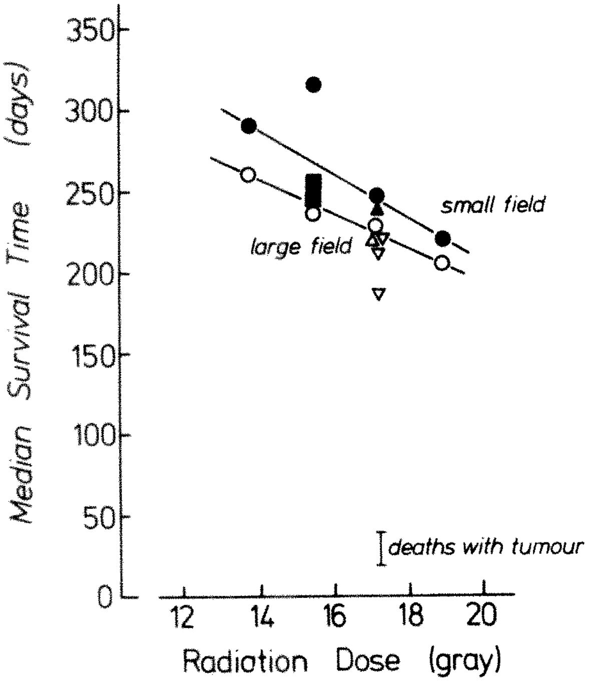

Fig. 3.

Median survival time of groups of mice irradiated with "large" (open symbols) and "small" (closed symbols) lung fields. The bar and triangles at 17.2 Gy show the survival of control and irradiated mice in the experiment shown in Fig. 2.

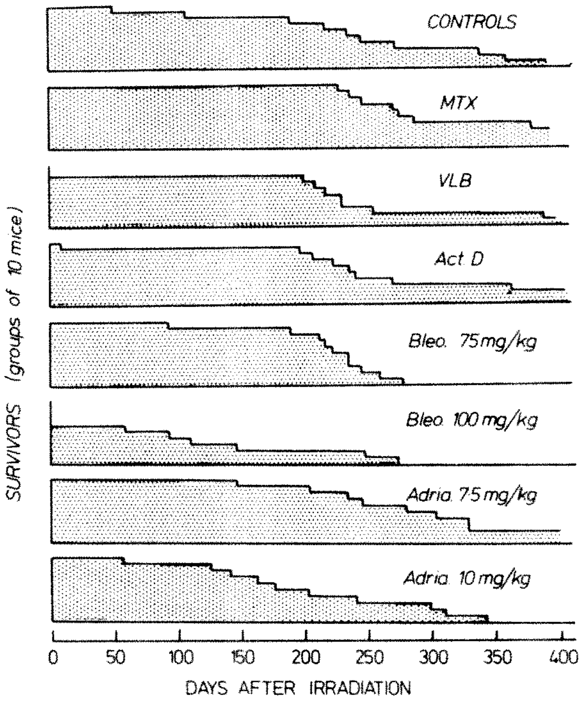

Fig. 4.

Survival of groups of ten mice treated with methotrexate (MTX), vinblastine (VBL), actinomycin (Act. D.) bleomycin (Bleo) or adriamycin (Adria) plus irradiation. Details given in Table I.

one early death following actinomycin D and four following the higher dose of bleomycin. Median survival times were calculated and are shown in Fig. 5. On the left of this chart the dose-dependance of survival following irradiation alone is shown. On the right are the results of the combined treatments. Within the scatter associated with groups of ten mice, it is probably only possible to conclude that the mice given higher doses of adriamycin and bleomycin, and both groups of cyclophosphamide-treated animals, showed a shortened lifespan due to the administration of drug.

Effect of misonidazole

In a pilot experiment on the effect of the radiosensitiser misonidazole (Ro–07–0582) on pulmonary damage, ten mice were given thoracic irradiation (15.5 Gy) 30 min after an intraperitoneal dose of 1 mg/g. They had a mean survival time of 157 days (S.D. 50) while ten mice given the same radiation dose without misonidazole survived for a mean of 218 days (S.D. 31). The difference between these means is significant at $p=0.05$.

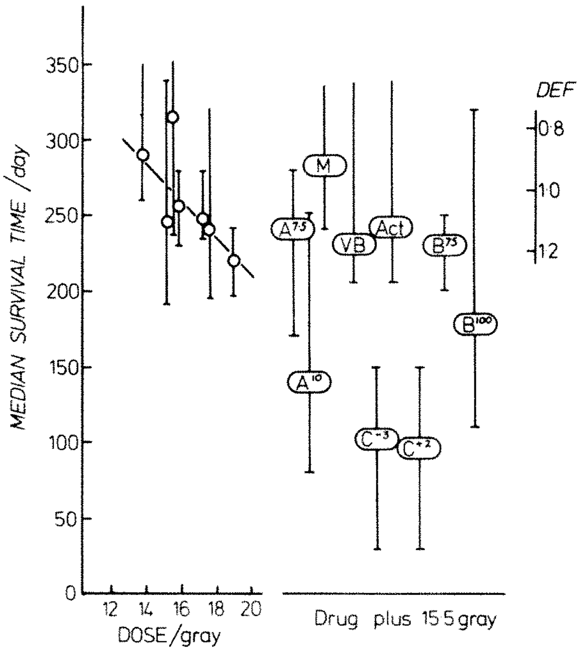

FIG. 5.

Median survival time of the groups of mice given chemotherapy plus irradiation (15.5 Gy). On the left are shown the dose-response data for the radiation alone and the scale on the right shows approximate dose enhancement factors from a dose of 15.5 Gy. The bar lines indicate the range of survivals of 6/10 of the mice. Table I gives the drug doses: methotrexate (M), vinblastine (VB), actinomycin (Act), bleomycin (B), adriamycin (A), cyclophosphamide at −3h (C^{-3}), cyclophosphamide at +2h (C^{+2}).

Effect of chemotherapy on radiation-induced skin reaction

The skin reactions observed in the present experiments were relatively mild, never exceeding a mean of 2.0 (early moist desquamation) for a group of ten mice scored at one time. As can be seen from the data in Table I, most treatments reduced the average skin reaction score, only bleomycin in high dose showing a tendency to increase it.

Comparison of the pattern of lung mortality in CBA mice

In view of the fact that death of C57Bl mice following thoracic irradiation occurred much later than has been reported in studies on other strains of mouse, an experiment with radiation alone was conducted on male CBA mice. These were also bred in the Institute animal unit that supplied the C57Bl mice.

The pattern of deaths at three radiation dose levels given with "large" field irradiation is shown in Fig. 6. The median day of death decreased from 125 days at 15.5 Gy to 96 days at 18.9 Gy. These results are comparable with those of Phillips *et al.* (1975) using LAF1 mice and Field *et al.* (1976) using TO mice.

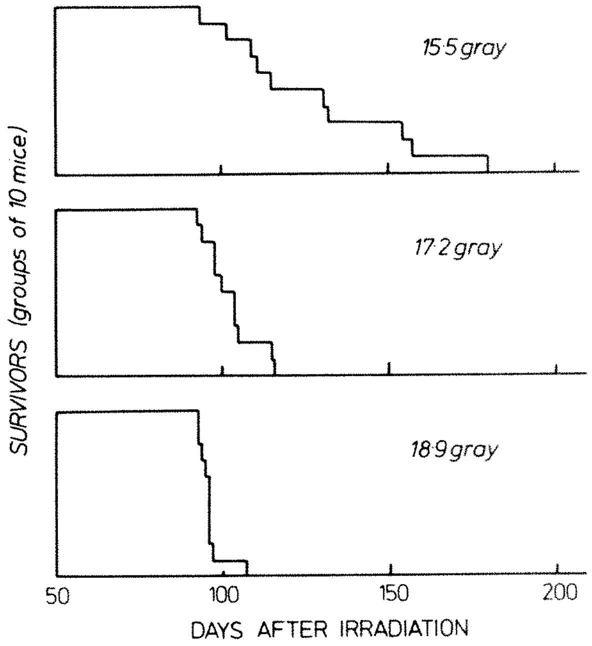

FIG. 6.

Survival of groups of ten CBA mice irradiated using the "large" field.

DISCUSSION

The present studies have revealed that the time-course of deaths in C57Bl mice following thoracic irradiation is considerably prolonged in comparison with other strains that have been studied. This does not mean that C57Bl mice are more resistant to thoracic irradiation, for the dose that gave 50% mortality was 12–13 Gy, similar to the value found by Phillips *et al.* (1975) and Field *et al.* (1976). What our results show is that C57Bl mice in this laboratory survive much longer before dying of what we believe to be pulmonary failure. Dr. T. A. Phelps in this department has found that C57Bl mice also live longer after whole-body irradiation than other strains before dying of intestinal failure. This strain difference in the timing of pulmonary failure is interesting in its own right and in subsequent studies we hope to investigate it further. From the point of view of our primary objective, which was to study the enhancement of radiation damage due to chemotherapeutic treatment, this property of C57Bl mice has forced us to use as end-point the median day of death following fixed doses of thoracic irradiation rather than obtaining dose-response curves in order to measure LD/50. Even so, each experiment has had a total duration of 400 days and the extent of our combined chemotherapy-radiotherapy experiments has therefore been limited. In our extension of this project, we propose to use CBA mice.

Our comparison of two sizes of thoracic field suggest that it is not critically important to irradiate the whole lung in studies of this type or to avoid extensive irradiation of tissues that lie just below the diaphragm. There was some difference in survival time between the two field sizes but it was not large. For studies with irradiation combined with drug treatment we elected to use the "small" field-size, in the belief that this more closely reflected clinical procedure.

The data that we have been able to acquire on the effect of chemotherapeutic treatment in modifying thoracic radiation damage are not extensive. They do indicate, however, the potentiating effect of high single doses of bleomycin or adriamycin given two weeks before irradiation and of cyclophosphamide given just before or just after irradiation. In spite of the very different pattern of deaths that we have seen, our data therefore confirm the enhancement of radiation damage with cyclophosphamide in mice seen by Phillips *et al.* (1975). Furthermore, the clinical observations that drug combinations which include adriamycin, bleomycin and cyclophosphamide increase the likelihood of radiation pneumonitis (reviewed by Phillips and Fu, 1976) are supported by the present work. Adriamycin presents a particular problem. As an agent that by itself can produce cardiac damage, there is good evidence both in animals and man that its toxicity to the heart is enhanced by irradiation (see Phillips and Fu, 1976). Since in our work the heart has been irradiated as well as the lungs, it is impossible to disentangle the effects of adriamycin and radiation on the whole cardiopulmonary system.

The pilot experiment with misonidazole gave a surprising result. This agent is thought to act as a radiosensitiser of hypoxic cells and as a cytotoxic agent in the presence of hypoxic cells. We would not have expected that lung tissue, even in anaesthetised mice, would have contained a significant proportion of hypoxic cells. A more extensive investigation of this phenomenon is now planned on CBA mice.

The skin damage results have been a useful by-product of the lung damage studies. Most of the chemotherapeutic agents that we administered reduced the radiation-induced skin damage. The apparent slight enhancement seen with cyclophosphamide is not in line with the more detailed studies that we have made with hind-leg irradiation (Steel *et al.*, 1978) and we are inclined to regard this as not significant. Although much further work remains to be done, and in our case it will be done with CBA mice, it seems likely that chemotherapeutic treatments can be found which, especially if separated in time from irradiation, will not seriously enhance radiation damage.

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Book reviews

The Human Pulmonary Circulation. By Peter Harris and Donald Heath. Second Edition, pp. xiv + 712, 1977 (Churchill Livingstone, Edinburgh), £28·00.
ISBN 0-443-01177-X.

This book differs from most largish volumes devoted to one field of knowledge in being written (rather than masterminded) by its two authors, and perhaps shows both the advantages and defects of this form of creation.

The lesser circulation is a complex and scientifically satisfying field of research. Complex, because of the interrelations of a low pressure circulation enclosed within the moving box of the thoracic cage. Our knowledge of the mechanisms of this system seem to be fairly comprehensive: it is this, the detailed, often mathematical description of the pulmonary circulation, which is the subject of this book.

Commencing with the anatomy of the pulmonary vessels, there are substantial chapters on measurements of pulmonary blood flow, blood volume, resistance, impedance and distensibility.

Pulmonary hypertension appears as the main theme in, or the second subject of, some fourteen chapters and is a central theme of this volume. The vascular changes associated with shunts are very fully covered, as are changes in pulmonary resistance in relation to hypoxia. Dietary pulmonary hypertension, giving experimental and clinical evidence concerning the induction of pulmonary hypertension was a new subject for me.

The clinical sections on pulmonary embolism and also on chronic lung disease seem a little thin in relation to their importance. It is interesting to note that the pulmonary circulation in acute infection receives no mention at all—pneumonia does not appear in the index. Any defects, like the strong points, are presumably reflections of the authors' points of view and interests. The most widely used clinical application of investigating the regional distribution of pulmonary blood flow is the radioisotope lung perfusion scan. This technique is referred to at various points, but never illustrated or described in detail (whereas a series of appendices cover such considerations as wedge pressure in veno-occlusive disease and the measurement of blood volume in a branching system).

Gross anatomy and radiological anatomy also receive rather scant attention. The only normal chest X-ray illustrated is one which appears in the first edition of 1962 and the comments concerning the radiological anatomy of pulmonary vessels are, I think, not true at the present time: it is possible to differentiate quite clearly between major pulmonary arteries and veins on a plain X-ray and this is also a very useful exercise.

These are, however, small points in a book which is both an excellent reference work, but also manages to be quite readable.

J. P. LAVENDER.

Textbook of Diagnostic Ultrasonography. By Sandra L. Hagen-Ansert., pp. ix + 493, 1200 illus. (including drawings by Eric P. Teichman) 1978. (The C. V. Mosby Company, St. Louis, Missouri Y. B. Medical Publishers). £28·25.
ISBN 0-8016-2011-2

The author of this book is a trained X-ray technologist who found radiography was not challenging enough. She therefore took the opportunity to learn and develop the use of ultrasound in diagnosis, starting in the days of A-mode techniques, and is now Educational Co-ordinator in the Division of Ultrasound of the Thomas Jefferson University Medical Centre, Philadelphia, with two-dimensional B-scanners, Doppler, real-time and echocardiographic equipment to help her. From her considerable experience in conducting national short-term ultrasound training programmes it became evident that there was a need for a comprehensive ultrasound textbook. She has therefore written this textbook with the assistance of 13 other contributors. It emphasizes anatomy, physiology, pathology and ultrasonic techniques and patterns. The book is divided into seven parts. Part 1 covers the basic principles of ultrasound, adequately describing the physics and some instrumentation. Part 2 is the largest and best section. It describes echocardiography comprehensively and it is well-illustrated. The abdomen is the subject of Part 3 and it includes the liver, gall-bladder and biliary system, paravertebral vessels, pancreas, retroperitoneum, suprarenal glands, kidneys and spleen. The pelvis is relatively briefly considered in Part 4 and this ranges through gynaecological conditions, normal gestation and obstetrical complications, fetal cephalometry and the placenta. The descriptions in this part are surprisingly superficial. In Part 5 the thyroid gland and non-imaging Doppler techniques are described. The text ends with two appendices which enumerate the attributes of a diagnostic ultrasonographer, and lays down guidelines for establishing a one year general ultrasound educational programme and also a specialized echocardiographic training programme. Finally an excellent bibliography up to 1977 is given. The text generally is adequate but there are unfortunately places where it is too simple, muddled or misleading. With the exception of Parts 1 and 2, there are far too many illustrations, with the result that they are displayed in too small a format and are therefore difficult to discern. They are presented positive and negative apparently at random, so much so that in several composite figures both presentations are used. To the inexperienced this must add to the difficulties of comprehending the subject. On the other hand the anatomical body sections at the beginning of Part 3 are helpful.

This book undoubtedly will have greater appeal to departments of ultrasound in the United States than in this country.

F. G. M. ROSS.

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Technical note

Reducing electron contamination of cobalt-60 teletherapy beams

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(Received September 1978 and in revised form March 1979)

One of the major advantages of megavoltage X and γ radiation in the treatment of deep-seated tumours is the skin-sparing effect, and it is widely recognized that this effect may be reduced or even destroyed if the radiation beam is significantly contaminated with secondary electrons. In telecobalt units such secondary electrons are produced predominantly through Compton interactions of the emitted photons with the source capsule and collimator. These energetic electrons can have energies up to about 1MeV, a maximum range of up to 0.5 g/cm^2, and are capable of reaching the skin surface where they will be absorbed in the first few millimetres of tissue thereby reducing the skin-sparing effect (Leung and Johns 1977; Smith and Sutherland 1976). Both these groups demonstrated that for small field sizes the contamination appears to be negligible. However, considerable contamination has been demonstrated with large field sizes, even with an air-gap of 15 to 20 cm between the skin surface and the end of the collimator system. The magnitude of the contamination is a function of the design of the source housing and collimator assembly. With some units a Perspex filter is provided by the manufacturer as an electron filter. Although this removes all the electron contamination incident on the filter, it is itself a source of secondary electrons and, as shown by Hanson and Grant (1976), real benefit may not always result, particularly if the filter is badly placed. Some method of quickly monitoring the extent of electron contamination is therefore very desirable.

Method

We have used a standard cylindrical ionization chamber, of 0.6 cm^3 volume, with graphite wall of thickness 0.085 g/cm^2 (Nuclear Enterprises Ltd Type 2500/3), to investigate the beam from a Gammatron S80 telecobalt unit (Siemens Ltd). By covering the chamber with increasing thicknesses of aluminium foil the electron component of the beam was gradually filtered out. The γ-ray response, as a function of foil thickness, was obtained by exposing the chamber to the purest γ-ray beam obtainable (small field size, large source-detector distance). Thus, knowing the magnitude of the γ-ray contribution to the exposure rate, the magnitude of the electron contribution could be found. The aluminium foils were curved into inverted U shapes and simply placed over the graphite wall and stem of the chamber, to provide effective filtering of the electron component while minimizing any backscatter from the γ-ray component. The "minimum thickness" is of course 0.085 g/cm^2, the inherent filtration of the graphite wall itself. Using this technique the ratio of the electron contribution to the photon contribution could be determined at any point in the beam.

Results

Electron contamination in the unfiltered beam was found to be almost linearly related to field size and to decrease proportionately with increasing source-to-detector distance (SDD). For sufficiently large field sizes, up to 80 cm SDD, the electron contribution to the exposure rate was found to exceed the photon contribution (Fig. 1).

The effect of this contamination on the build-up curve was investigated by embedding the chamber in the surface of a Mix-D/Perspex phantom to provide full backscatter, and covering it with layers

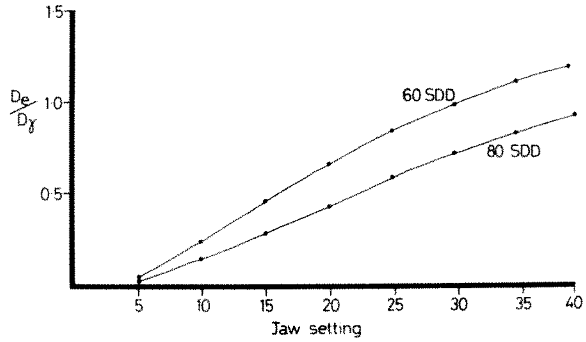

FIG. 1.

Ratio of electron to photon dose rate plotted against jaw setting for source-detector distances of 60 and 80 cm. The collimator system ended at 45 cm from the source. The jaw setting represents the field size (50% convention) at 80 cm source-skin distance. The inherent filtration of the chamber was 0.085 g/cm^2.

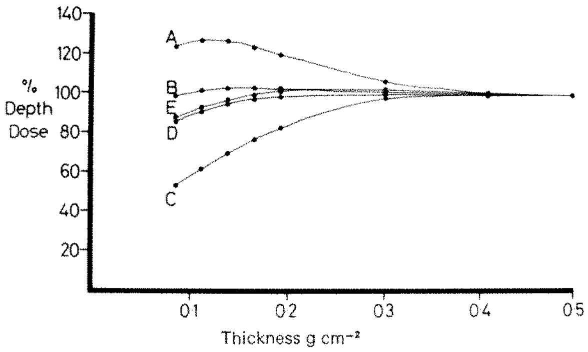

FIG. 2.

Percentage depth dose plotted against thickness of aluminium filter expressed in g/cm^2. Curves were normalized to 100% at the conventional build-up peak of 0.5 g/cm^2. (A) 60 cm SSD. Field size 40 × 40 cm at 80 cm SSD. (B) As A but with electron filter (3 mm Perspex). (C) 100 cm SSD. Field size 4.6 × 4.6 cm at 80 cm SSD. (D) As B but electron filter 0.51 g/cm^2 copper. (E) As B but electron filter 0.52 g/cm^2 lead.

of aluminium foil. The top sheet of Mix-D was "grooved" to accept the ionization chamber so that the centre of the chamber was co-planar with the top surface. The aluminium foils were pressed into close contact with the surface and chamber. Due to the thickness of the chamber wall the build-up curve could only be investigated at depths greater than 0.085 g/cm^2, but by using thin foils (0.027 g/cm^2) overdosage in the region between 0.085 g/cm^2 and the conventional build-up peak at 0.5 g/cm^2 was investigated.

The results are shown in curve A of Fig. 2 with the chamber positioned at the beam centre at 60 cm SSD and with a collimator setting of 40 × 40 cm (corresponding to the field size at 80 SSD). This combination of field size and SSD represents the worst possible case investigated for the unit. The results are presented with dose rates conventionally normalized to 100% at 0.5 g/cm^2 and an overdosage peak of 126% is seen to occur at a depth around 0.12 g/cm^2.

The Gammatron unit is supplied with a detachable 3 mm thick Perspex "electron filter" which can be fitted over the end of the collimator at a distance of 46 cm from the source. Curve B in Fig. 2 shows the effect of this filter on the build-up curve. With the filter in place the overdosage peak is reduced to 102% and the peak is moved to a depth around 0.16 g/cm^2.

Curve C in Fig. 2 is the build-up curve for a relatively pure photon beam obtained with a collimator setting of 4.6 cm × 4.6 cm and at 100 cm SSD. A further increase in SSD did not appreciably affect the shape of this curve. On comparison of curves B and C it is evident that there is still considerable electron contamination in the large beam filtered through the Perspex. By keeping the chamber position fixed and moving the filter closer to it, it becomes clear that the Perspex gives rise to an appreciable electron flux. It has been shown (Leung and Johns 1977; Smith and Sutherland 1976) that there is an optimum filter position which is quite close to the source, so that positioning the filter inside the collimator may be necessary to obtain the best build-up characteristics.

It has also been shown (Hine 1951) that equivalent thicknesses of medium atomic number filter materials produce fewer forward-scattered electrons than either low or high atomic number materials. Curve D in Fig. 2 shows the build-up curve obtained by replacing the Perspex filter by a copper one of thickness 0.51 g/cm^2. The copper is seen to produce a significant improvement compared with the filtering obtained using Perspex. Curve E in Fig. 2 shows the build-up curve obtained by using a lead filter of thickness 0.52 g/cm^2. This gives a build-up curve only slightly inferior to that of copper. A build-up curve for a tin filter was also measured but this did not show any significant difference from that obtained with a copper filter.

Conclusion

In conclusion, the problem of minimizing electron contamination is particularly relevant to modern telecobalt units which can provide large field sizes at relatively short SSD. This contamination may easily be estimated using a commonly available robust ionization chamber and a series of thin absorbing filters. If it is necessary to reduce contamination by the use of an electron filter in the beam, careful attention should be paid both to the material used for the filter and to its position.

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Case reports

Priapism: successful treatment and post-operative cavernosogram

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Priapism, a persistent painful erection of the penis, is treated by conservative or operative measures. Corpus cavernosography is the only radiological method for the objective assessment of the efficacy of operation.

A case of priapism was treated surgically, using a unilateral corpus cavernosum-saphenous vein shunt. The immediate and the late results were investigated by cavernosograms.

Case Report

A 26-year-old man was admitted to the Urology Clinic of the University of Athens for a persistent painful erection of the penis. His symptom had started 11 days before and was not related to sexual stimulation or desire.

The patient reported mild scrotal trauma 24 hours before the onset of the illness. There was no history of attacks of priapism in the past. Two years previously he had been operated on for hydatid cyst of the liver.

Conservative treatment had begun on the second day of the illness, including cold water enemas, tranquillizers, anti-coagulants, extradural anaesthesia and aspiration of the corpora cavernosa, but was not successful.

On admission the patient was in excellent general condition with normal temperature, pulse and blood pressure.

The penis was erect and very hard with engorgement confined to the corpora cavernosa, while the glans and the corpus spongiosum were of normal size and consistency. A mild haematoma was present in the scrotum. The laboratory tests and the rest of the clinical investigation failed to disclose any pathological findings.

Priapism persisted from the day of admission and therefore surgery was performed the next day, the 12th day of the illness. The method employed was similar to that described by Grayhack *et al.* (1964). It consists in the mobilization of the proximal 10–15 cm of the saphenous vein, which is then passed through an artificial subcutaneous tunnel reaching the root of the penis. The saphenous vein is subsequently anastomosed to the ipsilateral corpus cavernosum, giving free drainage to the blood stagnated in the penis. On completion of the operation the corpora cavernosa were drained by the artificial shunt, the erection gradually subsided and the penis became flaccid.

On the second post-operative day a cavernosogram was performed to check the function of the anastomosis. The method employed was that described by Hamilton and Swann (1967) with minor modifications. The cavernosogram (Fig. 1) showed satisfactory appearances of both corpora cavernosa. The point of anastomosis was clearly visible and so were the portion of the saphenous vein employed and the proximal femoral vein. No contrast medium was seen in the deep dorsal vein of the penis. Antibiotics and heparin were administered for five days after surgery. The patient had an uneventful post-operative course. It is noteworthy that erection reappeared upon finger compression of the anastomosed portion of the vein during the immediate post-operative period. Slowly erections started appearing with sexual excitement, but were not entirely satisfactory and persisted longer than normal. One month after the operation the saphenous vein could be felt on palpation, giving the feeling of a hard incomplete cord. In the meantime erections had improved. A second cavernosogram at this time showed considerable narrowing of the saphenous vein at several points, more marked in the area of the anastomosis (Fig. 2). The femoral vein was not visible while there was satisfactory draining of the corpora cavernosa through the deep dorsal vein of the penis to the venous plexuses of the base of the penis, the prostate and the true pelvis.

Discussion

Priapism is a relatively rare syndrome resulting from diminished or completely obstructed outflow

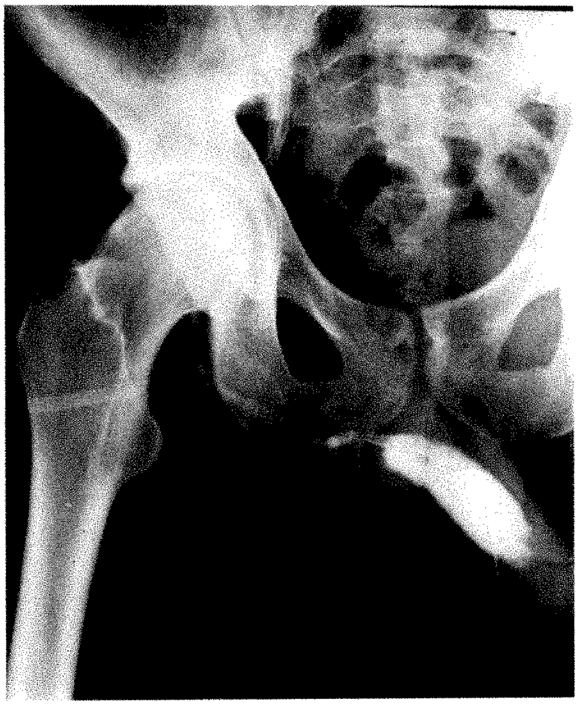

Fig. 1.

Cavernosogram two days after the operation demonstrates the point of anastomosis and the draining venous channels.

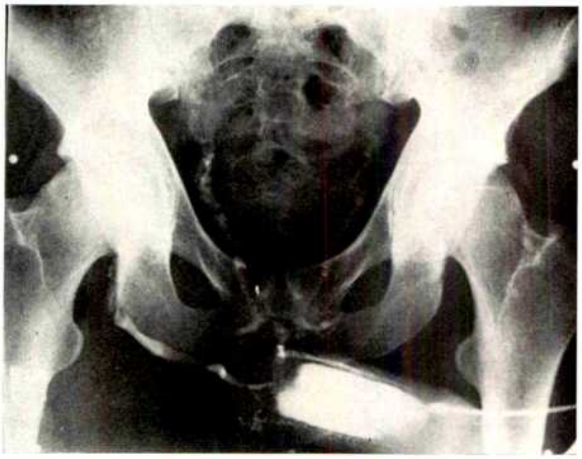

FIG. 2.

Cavernosogram one month after the operation. Multifocal narrowing of the anastomosed saphenous vein and free drainage through the recanalized deep dorsal vein of the penis.

from the corpora cavernosa through the deep dorsal veins of the penis below Buck's fascia. The glans and the corpus spongiosum appear intact because their draining superficial veins above Buck's fascia remain unaffected. The constant erection causes stagnation of blood and thrombosis within the vascular spaces of the penis, followed by fibrosis and impotence.

There are several factors that may be responsible for the venous thrombosis resulting in priapism: blood diseases such as sickle-cell anaemia, sickle-trait or chronic leukaemia, malignancy (either primary in the bladder, rectum or prostate, or metastatic malignancy), narcotics addiction, mental disorders, lesions of the central nervous system, etc.

In most instances the aetiological mechanism is not clear. In our case there was no underlying pathology, and the trauma to the scrotum and possibly to the base of the penis itself may have been the cause of venous thrombosis. Conservative treatment is generally unsuccessful. Catheterization of the bladder may be necessary because retention of urine may complicate the condition (Eadie and Brock 1970).

Surgical intervention is considered by most urologists (Garrett and Rhamy, 1966; Grace and Winter, 1968) to be the treatment of choice. The aim of the operation is to drain the blood from the corpora cavernosa and this may be achieved through a shunt connecting them with the corpus spongosium or an anastomosis with the long saphenous vein.

The operation must be undertaken as early as possible in order to preserve satisfactory function of the penis. Unilateral shunting is sufficient since the two corpora communicate extensively. A non-functioning shunt, usually the result of venous thrombosis, may necessitate a second shunt on the other side (Lee *et al.*, 1972) if recanalization of the deep dorsal vein does not appear. No complications of the operation have been reported except one case with pulmonary embolism presumed to have arisen from the saphenous-corpus by-pass.

Cavernosography is the radiological investigation opacifying the corpora cavernosa, whilst spongiography opacifies the corpus spongiosum (Fitzpatrick, 1973). In priapism where the former are involved, cavernosography may be indicated before and after surgery. It is not necessary to inject both corpora cavernosa as they fill equally and simultaneously with contrast medium when one is injected (Thomas and Rose, 1972; Edling and Leander, 1974). The introduction of the opaque agent is safe and painless and local anaesthesia is not necessary except with anxious patients. Flushing of the corpus cavernosum with heparinized saline is followed by removal of the needle and gentle pressure on the penis for a few moments. Cavernosography is an easy and useful investigation in cases of priapism.

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Case reports

Renal artery originating from the inferior mesenteric artery

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The arterial supply to the kidneys is variable. Many papers have been written dealing with the blood supply to normal and congenitally abnormal kidneys (Anson *et al.*, 1936; Graves, 1956; Merklin and Michels, 1958; Olsson and Wholey, 1964). Variations in the number of renal arteries are very frequent and, indeed, a single renal artery may be present in only 33% of normal subjects (Anson *et al.*, 1936; Gillaspie *et al.*, 1916). The origin of accessory renal arteries may be from the aorta or from other vessels. The latter variation has been infrequently mentioned in the anatomic or radiologic literature (Anson *et al.*, 1936; Gillaspie *et al.*, 1916; Merklin and Michels, 1958). In this paper, we report an extremely rare anomaly in which a renal artery originated from the inferior mesenteric artery in a normally-positioned kidney. We believe that this is the first time such an anomaly has been demonstrated by selective arteriography.

Case Report

A 22-year-old white male was admitted for evaluation of hypertension discovered during a routine physical examination. Except for the elevated blood pressure of 160/130 mm Hg, the physical examination was entirely within normal limits. Workup at our institution included routine laboratory investigations which showed no abnormalities. An intravenous pyelogram was obtained which revealed smooth enlargement and rounding of the lower pole of the left kidney (Fig. 1). Abdominal aortography and selective renal arteriography, as well as sampling of renal veins for renin assay, were then performed to rule out the possibility of renovascular hypertension. The aortogram revealed that the right kidney was supplied by two arteries originating from the aorta at the level of T12-L1. The left kidney was also supplied by two arteries. The main one originated opposite to the right renal arteries and the "plump" lower pole was supplied by a rather large branch originating from the inferior mesenteric artery (Fig. 2). This was confirmed by selective inferior mesenteric arteriography (Fig. 3). No renovascular cause for his hypertension was found and the patient was discharged.

Discussion

Aortic origin of renal arteries from as high as the level of T11 has been reported (Doppman, 1967). Renal arteries originating from the distal aorta, or the common iliac or hypogastric arteries, are frequent in malrotated, ectopic and congenitally abnormal kidneys. Renal arteries originating from visceral branches of the aorta have been described on only a very few occasions, mostly in the anatomic literature. Anson *et al.* (1936) in an anatomic study of the blood supply to about 400 kidneys mentions that arteries to ectopic kidneys "may originate from the inferior mesenteric artery", but he does not provide illustrations for such findings. Also he does not state if the arteries originating from the inferior mesenteric artery are to the upper, middle, or lower portions of the kidneys. Gillaspie *et al.*, (1916) describe a case of an upper pole artery originating from the coeliac axis which was seen during anatomic

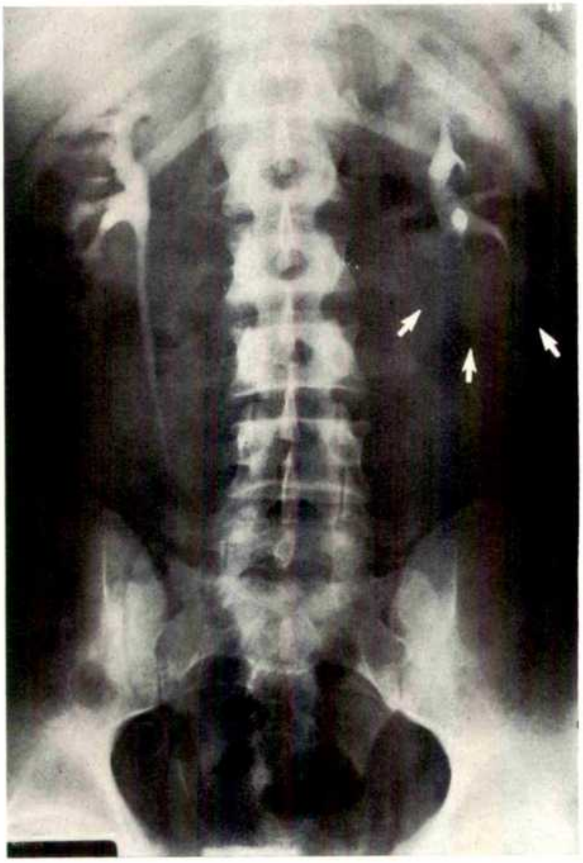

Fig. 1.

Excretory urogram reveals slight enlargement of the lower pole of the left kidney (arrows).

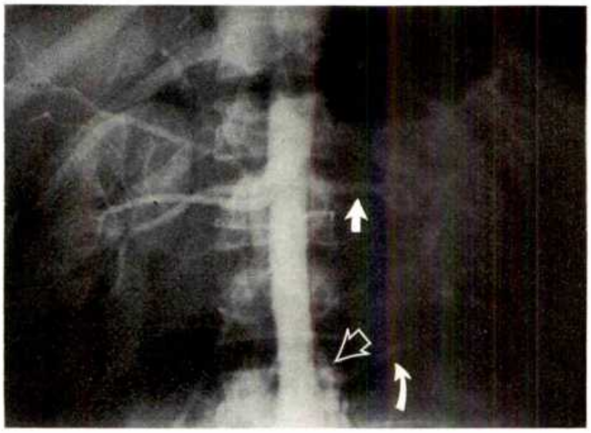

FIG. 2.

Midstream aortogram. There are two arteries to each kidney. On the right, they are of similar calibre and arise close to each other at the level of T12-L1. On the left, the main artery (arrow) originates from the aorta opposite to the upper right artery. The accessory lower pole artery (curved arrow) originates from the inferior mesenteric artery (open arrow). Incidentally, the right hepatic artery arises from the superior mesenteric artery.

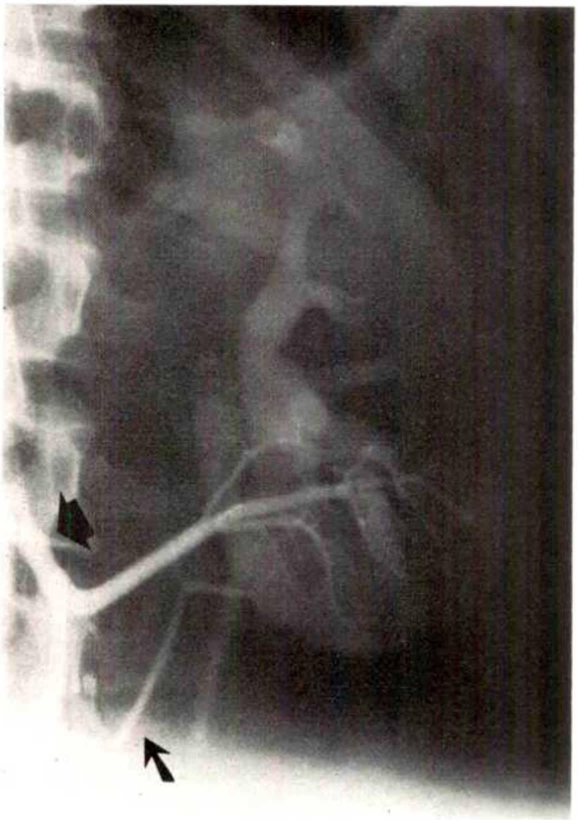

FIG. 3.

Inferior mesenteric arteriogram (arrowhead) demonstrates a large branch supplying the lower pole of the left kidney and the left colic artery (arrow)

dissection, but again there are no illustrations. One case of an upper pole artery arising from the superior mesenteric artery was described by Merklin and Michels (1958) in their excellent review of the variants of the renal arteries, based upon the dissection of 185 kidneys and from a review of the literature including reports on the blood supply to about 11,000 kidneys. Blood supply to the lower poles of both kidneys from a common trunk originating from the aorta and bifurcating to supply both kidneys was reported by Levine (1970). Two single cases of renal arteries supplying normally located kidneys, originating from the contralateral renal artery, have been reported (Jeffery, 1972; Libshitz *et al.*, 1972). Contralateral supply in cases of horseshoe, "dumbbell", or crossed ectopic kidneys have been reported with relative frequency (Olsson and Wholey, 1964).

In the case reported herein, the supply to the lower pole of the left kidney originated from the inferior mesenteric artery. This is an extremely rare anomaly. No similar case has ever been reported in the angiographic literature. In the reports of Gillaspie *et al* (1916) and Merklin and Michels (1958), the anomalous arteries originated from the superior rather than the inferior mesenteric artery and supplied the upper pole of the kidney rather than the lower pole.

The kidneys develop through three stages: pronephros, mesonephros and metanephros. They originate in the pelvis and ascend upward and rotate to occupy the lumbar region. At the mesonephric stage, the kidneys acquire their blood supply from branches of the aorta originating from the level of the second cervical to the second lumbar segments. There are from 20–30 segmental mesonephric arteries on each side constituting the rete arteriosum urogenitale (Gillaspie *et al.*, 1916; Graves, 1956). As the mesonephros degenerate and the metanephros develops, only the more caudal mesonephric vessels remain.

Early in embryological development, the inferior mesenteric artery originates from the aorta by several roots, many of which are anastomosed with or constitute part of the rete arteriosum urogenitale (Bremer, 1915). Multiple renal arteries thus represent persistence of mesonephric vessels. Renal branches originating from the iliac, inferior mesenteric or middle sacral arteries, or distal aorta, represent persistence of the more caudal branches of the vascular network supplying the kidneys (Anson *et al.*, 1936; Bremer, 1915; Graves, 1956). This network is so complex that it is not surprising that accessory renal arteries are, in general, fairly common. It is difficult to explain, however, why the anomaly being reported is so rare. Recognition of this anomaly is of obvious clinical importance to the surgeon.

ACKNOWLEDGMENT

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Scintigraphic demonstration of an intrahepatic gall-bladder presenting as a focal liver lesion

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When a conventional liver scintigram shows a localized intrahepatic defect, additional scintigraphy with ^{99}Tc^{m}-diethyl-acetanilid-iminodiacetate (HIDA) can help to distinguish lesions caused by dilated bile ducts and gall-bladder impressions from parenchymal lesions. The present case is an example of an intrahepatic gall-bladder (Swart, 1976) presenting as a defect of colloid uptake in the right lobe of liver (Chang, 1976; Blanton *et al.*, 1974).

CASE REPORT

A 77-year-old white female with known chronic active hepatitis was referred for liver studies. A sulphur colloid scintigram showed a shift in spleen/liver ratio and slight enlargement of the left lobe of liver. There was a focus of decreased uptake of colloid in the right lobe compatible with a hepatoma (Fig. 1). Hepatobiliary scintigraphy with ^{99}Tc^{m} HIDA, however, showed a region of increased uptake corresponding with the area of decreased uptake of colloid suggesting that the focus was filled with bile (Fig. 2). An intravenous cholecystogram (Fig. 3) confirmed the intrahepatic location of the gall-bladder.

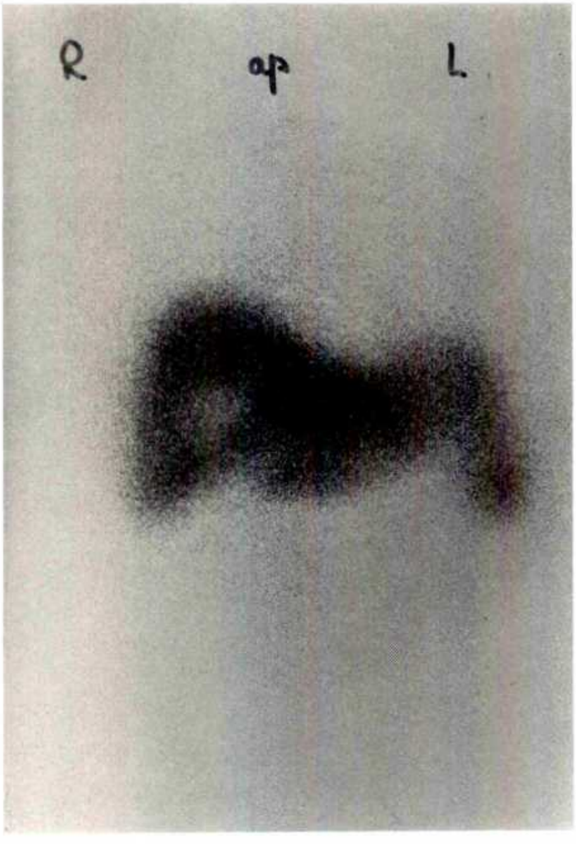

FIG. 1.

Colloid scintigraphy of the liver 15 minutes after intravenous injection of 1 mCi ^{99}Tc^{m}-S-colloid. Focal decreased uptake in the right lobe.

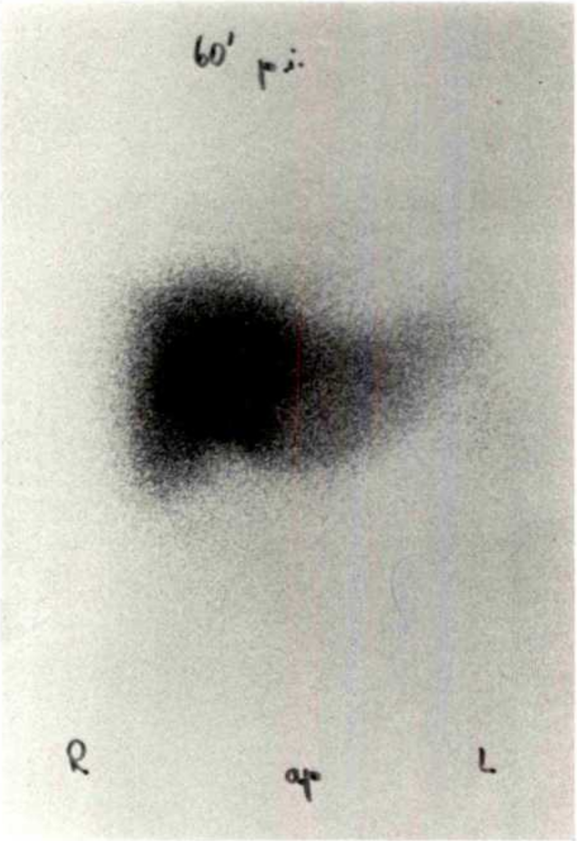

FIG. 2.

Hepatobiliary scintigraphy by intravenous injection of 5 mCi ^{99}Tc^{m} HIDA, 60 minutes pi. Rounded increased uptake.

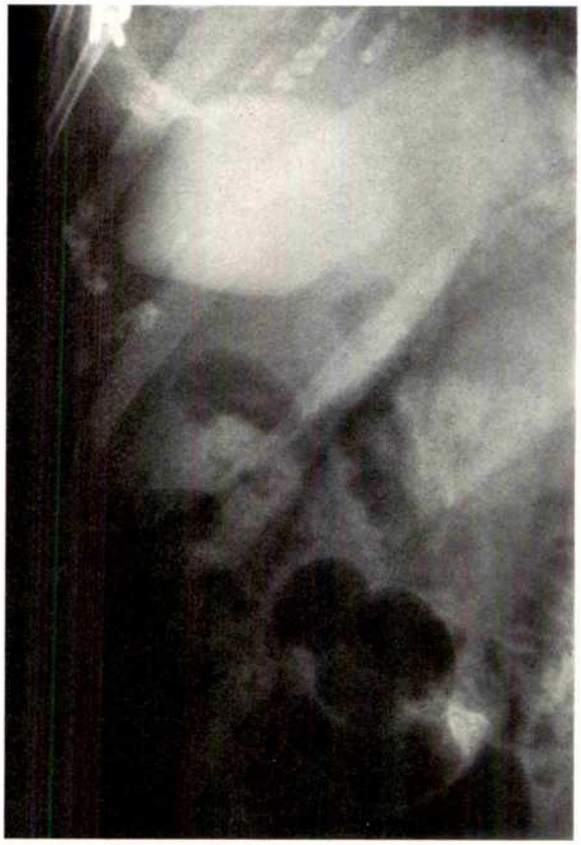

FIG. 3.

Intravenous cholecystogram shows an intrahepatic gallbladder.

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BLANTON, D. E., BREAM, C. A., and MANDEL, S. R., 1974. Gallbladder ectopia, a review of anomalies of position. *American Journal of Roentgenology*, *121*, 396–400.

Book review

Kleinhirnbrückenwinkel-tumoren: Diagnostic and Therapie. Edited by: D. Plester. S. Wende and N. Nakayama, pp. ix+282, 181 illus., 1978. (Springer Verlag; Berlin and New York), DM 148/$74.00
ISBN 3-540-08546-7

This small monograph concerns the diagnosis and treatment of tumours of the cerebello-pontine angle. There are contributions by some fifteen international authors, including neuroradiologists and neurosurgeons. All aspects of the diagnosis of C.P. angle tumours are discussed. The only British author is Dr. Burrows who covers isotope scanning. Unfortunately CT scanning which is now perhaps the most important investigation of all, has only four or five pages devoted to it. This is surprising in a book published in 1978 since such aspects as Myodil cisternography and vertebral angiography are very well discussed in great detail. The illustrations are all of excellent quality and apart from the major omission mentioned above, the book should prove useful to neurosurgeons and neuroradiologists, though some knowledge of German is required.

DAVID SUTTON.

1979, *British Journal of Radiology*, 52, 756–758

Short communications

Mediastinal lymphoscintigraphy reflects cell kinetics of developing malignant ascites

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A number of observations suggest that ascitic tumour cells are capable of occluding lymphatic channels in the diaphragm and that this occlusion leads to the development of ascites (Allen and Raybuck, 1960; Hirabayashi and Graham, 1970; Fastaia and Dumont, 1976; Bronskill *et al.*, 1977). For example, Holm-Nielsen (1953) showed that, while the absorption of particulate material through the diaphragmatic surfaces of mice with carcinomatous ascites was negligible, control mice showed diffuse mottling of diaphragmatic surfaces and substernal lymphatics. In mice bearing intraperitoneal (i.p.) tumour cells, Feldman *et al.* (1972) found diminished egress of labelled erythrocytes from the peritoneal cavity as well as tumour cell invasion of diaphragmatic lymphatics, before the development of frank ascites.

Based on these observations, we speculated that the onset of lymphatic blockade was related to the absolute number of i.p. tumour cells and that the rate of onset was dependent on the rate of tumour cell division.

Because the lymphatic channels of the diaphragm drain into the mediastinum, mediastinal lymph nodes (primarily those of the internal mammary chains) are normally visualized scintigraphically after the i.p. or subcostal injection of radiolabelled colloid; visualization does not

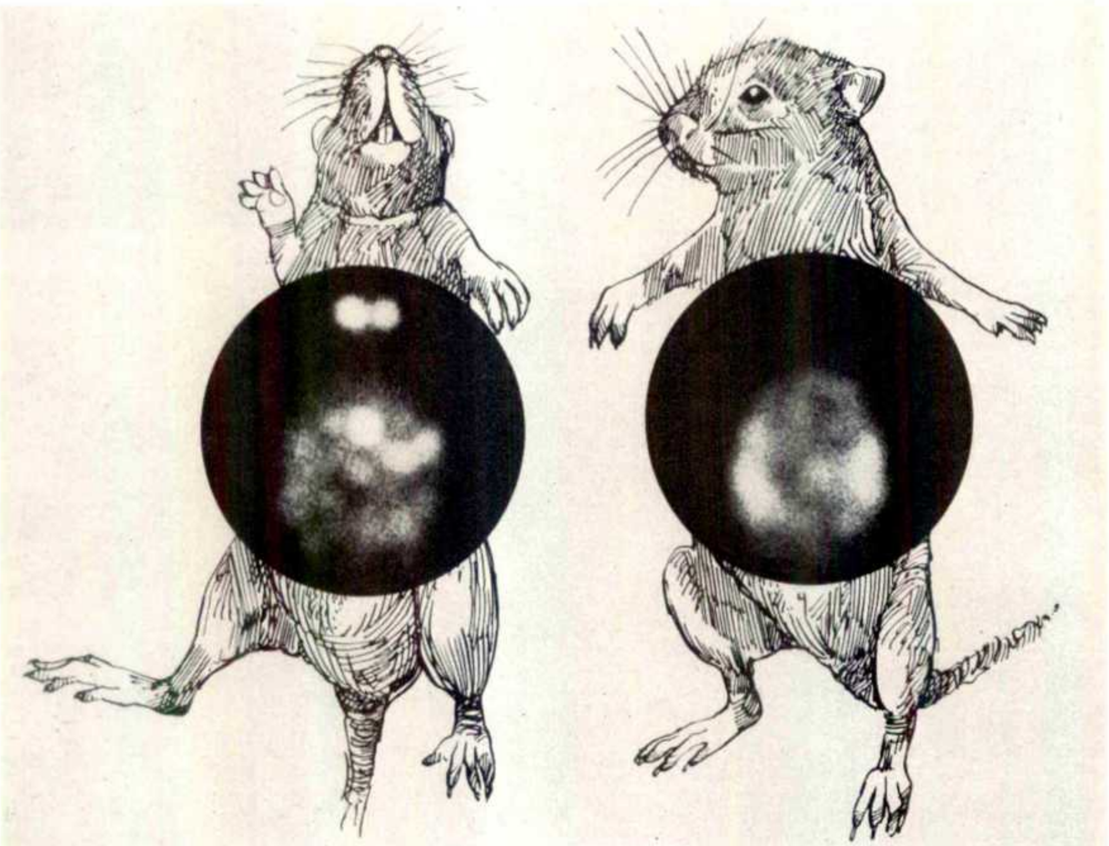

FIG. 1.

Representative mediastinal lymphoscintigrams. The animal on the left is a non-tumour bearing control; paired regions of activity are present within the mediastinum. The animal on the right had been injected with 10^6 tumour cells i.p. 1 day before study; there is no mediastinal activity. Equivocal mediastinal activity was observed only rarely.

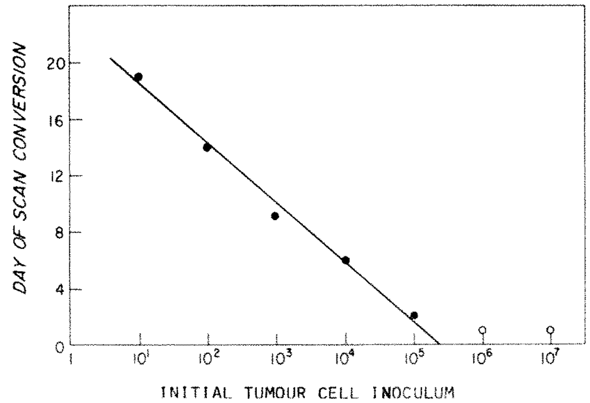

FIG. 2.

Lymphoscintigram conversion and initial tumour cell inoculum. Each point represents the average of two experiments, in each of which at least five mice were examined on an alternate day or daily basis during the period of predicted scan conversion. Scan conversion was usually complete within 2–4 days; the recorded day of conversion is the day of median scan conversion. The slope of the line and y-intercept were determined by semi-logarithmic linear regression analysis. The correlation coefficient is greater than 0·99.

occur, however, in the presence of overt ascites (Anghileri, 1968; Atkins *et al.*, 1970; Coates *et al.*, 1973; Ege and Bronskill, 1978). Moreover, normal mediastinal lymphoscintigrams are observed in ascites of non-malignant origins (Coates *et al.*, 1973). The mediastinal lymphoscintigram thus appeared to be a potentially sensitive indicator of incipient malignant ascites and a useful instrument for testing our hypothesis.

MATERIALS AND METHODS

The tumour used in these experiments arose spontaneously in the ovary of a C3H mouse (Fekete and Farringno, 1952) and has been maintained in its ascitic form by serial i.p. transplantation in female C3HeB/FeJ mice (Jackson Laboratory). A regular relationship has been observed between the size of the tumour cell inoculum and the rate of weight gain (Order *et al.*, 1973) as well as the median time to death (Bloomer and Adelstein, 1977).

Lymphoscintigraphy was performed two hours after the i.p. injection of 100–150 μCi ^{99}Tc^{m} sulphur colloid. Animals were sacrificed by cervical dislocation and scintigrams obtained in the anterior projection using a scintillation camera fitted with a pinhole collimator (Fig. 1).

The mean generation time of ascitic tumour cells was calculated at the time of lymphoscintigram conversion by the repetitive labelling method (Steel, 1977). Mice were injected i.p. with 10 μCi ^{3}H-thymidine at two hour intervals over a 10–12 hour period. Two animals were sacrificed 30 minutes after each injection, tumour cells harvested, washed, fixed in methanol: acetic acid (3:1) and dropped on to slides. Autoradiography was performed with NTB-2 nuclear track emulsion (Eastman Kodak).

RESULTS

The median day of lymphoscintigraphic conversion from visible to non-visible mediastinal activity was recorded as a function of the initial tumour cell inoculum (Fig. 2). A linear relationship was observed between the day of scan conversion and log initial tumour cell inoculum within the range 10–10^5 cells. The y-intercept of this line $(2.3 \pm 0.2) \times 10^5$ cells, is presumed to be the minimum number of tumour cells necessary for scan conversion to occur. Thus, when cells exceeding this number (10^6 or 10^7) are inoculated, conversion of the lymphoscintigram is observed within one day. No weight gain or ascites was detected in mice at the time of scan conversion nor was there any microscopic evidence of tumour invading diaphragmatic tissue at the time the scans changed.

TABLE I

GENERATION TIMES AT LYMPHOSCINTIGRAM CONVERSION IN TUMOUR BEARING MICE

Initial tumour cell concentration	Day of scan conversion	Generation time* (h) at day of scan conversion
10^1	19	21
10^2	14	30
10^3	9	23
10^4	6	20
10^5	2	17

*Mean ± SD = 22 ± 5

Additional studies were undertaken to confirm the observation that the conversion of mediastinal lymphoscintigrams was related to the presence of a critical number of tumour cells. First, silica particles in the range of 5–20 μ were injected i.p. and lymphoscintigraphy performed one and two days later. There was no conversion of lymphoscintigrams with silica doses of 10–60 mg despite the fact that toxicity was observed when the amount of silica injected exceeded 30 mg. Second, because this tumour is antigenic (Order *et al.*, 1973) and appears to elicit an intense inflammatory response in diaphragmatic tissue (Feldman, 1975), mice were treated with 5 mg hydrocortisone i.p. twice daily for 1–4 days before injection of 10^6 tumour cells. This anti-inflammatory treatment failed to prevent scan conversion 24 hours later and is consistent with our hypothesis that scintigraphic conversion is dependent on tumour cell burden.

If scan conversion takes place when tumour cells exceed a critical number, the mean population doubling time (30 ± 1 h) can be estimated from the slope of the straight line in Fig. 2, i.e. from the time it takes a given tumour cell inoculum to reach this critical size. To compare this value with that obtained by a more traditional method, we performed repetitive labelling experiments (Steel, 1977) on the day of scan conversion for tumour cell inocula of 10–10^5 cells (Table I). The mean generation time obtained in this manner is 22 ± 5 h. The fraction of labelled cells reached a plateau at 0·8–0·9, suggesting the presence of non-cycling or quiescent cells and/or heterogeneity of tumour cells, some of which have very long cell cycle times (Frindel *et al.*, 1969; Tannock, 1969). Although not generally considered an important factor in early ascites (Steel, 1968), cell loss may also be present. Both quiescent cells and cell loss would be expected to lengthen the population doubling time observed by lymphoscintigraphy.

DISCUSSION

Although it is surprising that a binary all-or-none visualization of mediastinal lymphatics should yield reliable quantitative estimates, these experiments demonstrate that mediastinal lymphoscintigraphy is a very sensitive and possibly specific indicator for small numbers of i.p. tumour cells. Moreover, it appears that scan conversion can be used to predict *in vivo* the cell kinetics of developing malignant ascites. Thus, it is possible that lymphoscintigraphy may have special significance in the clinical evaluation of patients with ovarian cancer not only as a diagnostic test for early peritoneal dissemination (Ege and Bronskill, 1978) but also as a marker for assessing the kinetics of tumour cell division and the response to treatment.

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Simplified cell labelling with indium-111 acetylacetone

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(Received April 1979)

Isolated cells labelled by means of ^{111}In-oxine (8-hydroxyquinoline) have been found clinically acceptable for the diagnosis of abscesses (Thakur *et al.*, 1977) and vascular thrombi (Goodwin *et al.*, 1978), as well as useful in research on cell migration and survival in animals (Rannie *et al.*, 1977) and man (Lavender *et al.*, 1977).

Attention has recently been drawn to the detrimental effect this method of labelling may have on cells (Segal *et al.*, 1978; Danpure *et al.*, 1979; Silvester 1979). In part, damage is attributable to the soft radiation (Auger electrons) emitted in the decay of intra-cellular ^{111}In, but further damage may also be caused by a too-high oxine concentration, or by the presence of heavy-metal impurities.

With care these problems may be overcome, but a further hazard remains: the ^{111}In-oxine complex is prepared and dispensed in ethanol solution, which itself can be toxic when added to the washed-cell suspensions (Atkinson *et al.*, 1977), and which it is inconvenient to store and handle.

We wish to draw attention to a technically simpler method of labelling cells which overcomes this hazard. This uses acetylacetone, in place of oxine, to form a lipid soluble complex which is also soluble in physiologically acceptable aqueous buffer solutions.

The method was first reported (Sinn *et al.*, 1974) for labelling erythrocytes, and was included in the survey of radioactive agents for *in vitro* labelling of phagocytic leukocytes by McAfee and Thakur (1976), but despite an apparently encouraging result the latter authors preferred subsequently to develop the use of the oxine complex. We have recently extended the use of the ^{111}In-acetylacetone (^{111}In-acac) complex to label isolated lymphocytes, granulocytes, platelets and HeLa cells. Our studies on the viability of these cells after labelling will be reported in detail elsewhere, but for present purposes it can be stated that we find ^{111}In-acac no more damaging to cells than ^{111}In-oxine, and considerably easier to prepare and use.

MATERIALS

(A) ^{111}In Cl_3 solution. "Carrier-free" $^{111}InCl_3$ in 0.04 M HCl, 10 mCi/ml, sterile solution (the Radiochemical Centre, Amersham).

(B) HEPES-buffered acetylacetone. 5 ml 2 M HEPES (N-2-hydroxyethylpiperazine-N^{1}-2-ethanesulphonic acid) (Hopkin and Williams). 4.02 g NaCl, 5.7 ml 1 M NaOH, 0.95 ml acetylacetone (Sigma or E. Merck). Water for injection to 500 ml: final adjustment to pH 7.6 by dropwise addition of NaOH.

(C) TRIS-buffered acetylacetone. 15.5 ml 1 M TRIS (Tris (hydroxymethyl) aminomethane) (E. Merck). 0.30 ml acetylacetone, 1 M HCl to bring pH to 7.6. Water for injection to 100 ml: final adjustment to pH 7.6 by dropwise addition of HCl.

N.B. Solutions (B) and (C) are pale straw-yellow in colour. They are sterilized by millipore filtration and stored in the dark at 4°C.

Method

Because the labelling step is non-selective, the specific cell (or platelet) population which it is desired to label must first be isolated, just as it is when using the ^{111}In-oxine complex, by one of the several published methods. After the separation step, the cells are washed free from residual plasma and resuspended, normally in about 2 ml of the chosen buffer solution. (HEPES is preferred by our British colleagues when labelling white blood cells or tumour cells, TRIS by our German colleagues when labelling platelets.)

Meanwhile a stock solution of the ^{111}In-acac complex is prepared by adding an appropriate amount (usually 100 μl) of $^{111}InCl_3$ solution (A) to 1 ml of HEPES- or TRIS-buffered acetylacetone (B) or (C). (Such solutions have been stored in a refrigerator, and used over a period of several days.)

Labelling is achieved by adding the required volume of this solution to the separated cells suspended in the corresponding buffer solution and mixing gently before standing for ten minutes at room temperature. After this an equal volume of plasma is added, to remove any ^{111}In which is not bound by this time within the cells, the suspension is centrifuged, the supernatant solution removed, and the cells then resuspended in plasma for reinjection. The fraction of ^{111}In which is bound in the cells at this stage depends to a large extent on the number of cells being labelled, but should be in the range of 70–80%.

Discussion

The success of clinical investigations carried out with ^{111}In-labelled cells will always depend most critically upon the care with which the cells themselves are handled, but the use of acetylacetone as the ^{111}In-complexing agent, instead of oxine, eliminates at least one agent, ethanol, which is potentially damaging. Furthermore, unlike the preparation of the ethanolic ^{111}In-oxine which requires solvent extraction into chloroform and the removal of chloroform by evaporation before final dissolution in ethanol, the preparation of an aqueous ^{111}In-acac solution is a simple one-step operation.

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Book review

Ultrasound in Tumour Diagnosis. Edited by C. R. Hill, V. R. McCready and D. O. Cosgrove, pp. vii+285, 1979, (Pitman Medical Publishing, Kent) £11·00.
ISBN 0-272-79435-X.

This is an excellent book. The editors are to be congratulated on achieving in considerable measure their aim of critically documenting the existing applications of ultrasound in cancer management.

The authors of the 14 chapters are all well known authorities. The standard is consistently high, both up-to-date and readable. In the main the illustrations are of good quality, although a few bistable images do appear. It is a pity that in the chapter on renal tumours the images are all negatives which do not appear to have reproduced as well as the positives used in the rest of the book.

The core of the book consists of a series of chapters dealing with a particular anatomical region. This is sandwiched by introductory chapters on the historical development of the subject, which makes fascinating reading, and a summary of the technology of modern equipment. The book then concludes with a chapter on ultrasonically guided biopsy, tissue characterization and a perspective of the place of ultrasound in relation to other diagnostic modalities.

In what remains a comprehensive book I was surprised to see the omission of a chapter on the lymphomas, however it is always easy to point to omissions by way of criticism.

This is certainly the first book to summarize so fully the subject of ultrasonic tumour diagnosis. It is informative and makes excellent reading. I strongly recommend it to all those with an interest in this field. It is particularly good value at the price.

K. C. Dewbury.

1979, *British Journal of Radiology*, 52, 760–761

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Grey-scale ultrasound demonstration of ureterocele and hydroureter

THE EDITOR—SIR,

Dr. Nikapota (Nikapota and Wray, 1978) rightly draws attention to the use of ultrasound in the demonstration of dilated ureters. He writes that this is almost always difficult in the supine position due to overlying gas-containing loops of bowel. Whilst this is true of normal ureters, dilated ureters on the other hand are often well shown in the supine position provided that a very full bladder is available for use as an ultrasonic window. They are then seen as tubular, transonic structures that enter the pelvis immediately anterior to the sacrum, follow a curvilinear course midway between the sacrum and bladder, and finally enter the bladder postero-inferiorly. They are better shown in longitudinal than transverse sections. I enclose three examples to illustrate these points.

The first patient's renal function was so poor that the ureters could not be convincingly demonstrated by con-

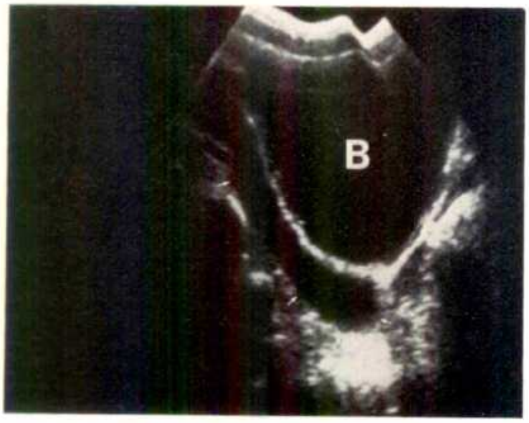

FIG. 1.

The dilated ureter (arrowed) is shown. Its distal portion is clubbed. The gap between the ureter and bladder (B) represents the undilated portion of the ureter which contains no urine.

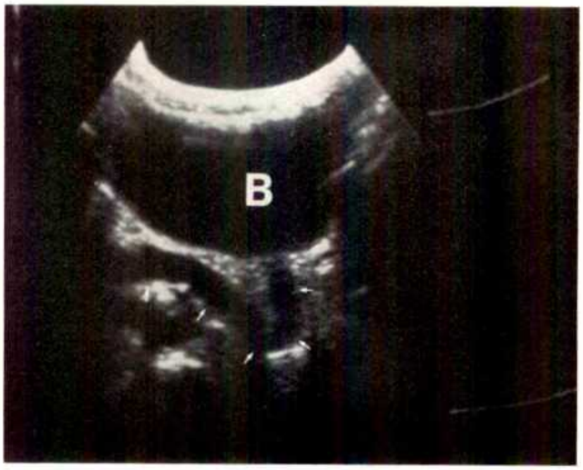

FIG. 3.

The right ureter in longitudinal section. Note the "fish-hook" appearance.

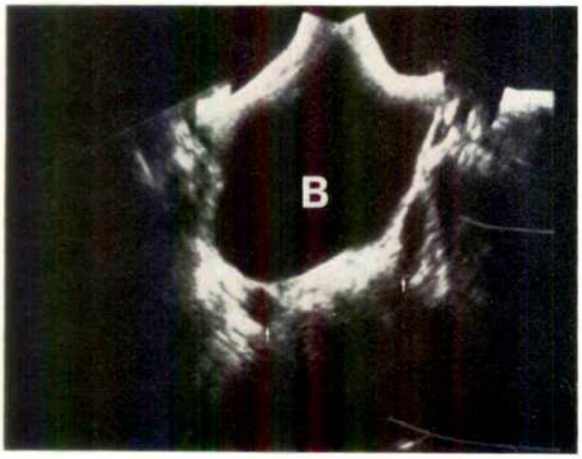

FIG. 2.

The ureters (arrowed) are seen in cross-section behind the bladder (B).

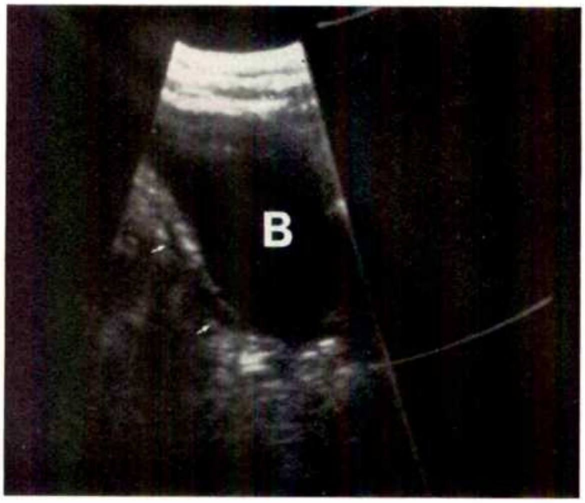

FIG. 4.

A scan along the line of the ureter. The scan was performed at approximately 45 deg to the sagittal plane.

ventional radiography. Ultrasound showed a dilated left ureter and a very large right ureter (Fig. 1). A right antegrade pyelogram was performed. This showed a megaureter.

The second patient was referred for investigation of "pancreatic calcification". Ultrasound showed bilateral hydronephrosis, and left renal calculi. Both ureters were well seen in transverse and longitudinal section (Figs. 2 and 3).

The third patient, a young girl, had falling renal function following a recent transplant. Ultrasound demonstrated a normal transplant ureter thus excluding obstructive uropathy (Fig. 4). The features of acute rejection were noted in the transplanted kidney.

In all three cases the ureters can be seen to enter the bladder from behind in the region of the bladder base. It is therefore hard to accept that the structure labelled "ureterocele" in Dr. Nikapota's article is anything other than a collection of bowel shadows. Indeed, even allowing for some loss of detail in the reproduction, careful scrutiny of Fig. 2 shows that a similar appearance is present immediately above the "ureterocele". Simple ureteroceles arise at the normal ureteric orifice a site that corresponds to the top of the structure labelled "diverticulum". Furthermore the ultrasound appearances of ureteroceles have already been described. Typically a "cyst within a cyst" is seen (Pollack and Goldberg, 1977).

Yours, etc.,
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Grey-scale ultrasound demonstration of ureterocele and hydroureter

THE EDITOR—SIR,

In the case report demonstrating a ureterocele and hydroureter in your December, 1978 issue (Nikapota and Wray, 1978), the authors have shown the ureter entering the bladder close to the summit. We have examined a significant number of patients with dilated ureters and these are usually identified in a more posterior position entering the bladder much lower down. It is unlikely that an ectopic ureter would enter the bladder in the position shown and in the absence of surgical and autopsy confirmation I would question the interpretation of the ultrasonogram.

Yours, etc.,
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REFERENCE

NIKAPOTA, V. L. B. and WRAY, M. I., 1978. Grey-scale ultrasound demonstration of ureterocele and hydroureter. *British Journal of Radiology*, *51*, 1016–1018.

The $Z^{2.94}$ "rule"

THE EDITOR—SIR,

The recent letter of reply by Jones (1979) will, I hope, "nail the coffin shut" on the $Z^{2.94}$ "rule" for determination of the effective atomic number of compounds and mixtures. Numerous authors (*e.g.* McCullough, 1975; White, 1977; Rutherford *et al.*, 1975) have developed a Z^m dependence for the electronic cross-section of the photoelectric effect in "soft tissue" materials (*i.e.* $6 \leqslant \bar{Z} \leqslant 8$), where m is usually between 3.5 and 3.8, not 2.94 as widely used. The tenacity of the $Z^{2.94}$ rule is illustrated by the fact that it has appeared within the last month in three manuscripts I have reviewed and, in all cases, the "disagreements" that the authors went to great pains to explain away were easily clarified when a more appropriate variation of Z^m was assumed.

Yours, etc.,
E. C. MCCULLOUGH.

Mayo Clinic/Foundation,
Rochester, MN 55901, USA.
(*Received June 1979*)

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1979, *British Journal of Radiology*, 52, 762–765

Proceedings of The British Institute of Radiology

New radiopharmaceuticals including iodine-123

Abstracts of papers read at The British Institute of Radiology meeting held at the Edward Lewis Theatre, Middlesex Hospital Medical School, London W1 on February 14, 1979.

Approaches to tumour localization with technetium 99m labelled liposomes, by R. F. Jewkes, K. Jeyasingh and V. Richardson.
New lamps for old—a re-evaluation of some failed adrenal imaging agents, by G. S. Boyd and M. V. Merrick.
Technetium 99m radiopharmaceutical kits—in-house or commercial?, by A. M. Millar.
Lung uptake of liver scanning agents, by T. McCarthy.
The comparative pharmacology of technetium IDA derivatives, by P. H. Cox.
The production of iodine 123, by J. G. Cuninghame.
Clinical practice with iodine 123, by K. E. Britton, C. C. Nimmon, A. Fountos, B. Shapiro, S. Londres and A. T. Elliott.
Pharmaceutical experience with iodine 123, by L. A. Hawkins, L. J. Dyke and A. T. Elliott.
Iodine 123 in the investigation of renal disease, by H. J. Testa.
Iodine 123-iododeoxyridine: a potential indicator of tumour response to treatment? by A. B. Robins and D. M. Taylor.

APPROACHES TO TUMOUR LOCALIZATION WITH TECHNETIUM 99M LABELLED LIPOSOMES

By R. F. Jewkes, K. Jeyasingh and V. Richardson

Department of Nuclear Medicine, Charing Cross Hospital and Department of Biochemistry, Charing Cross Hospital Medical School, London W6

Liposomes of different charges, negative (P:C:D, 7:2:1),* neutral (P:C, 8:2) and positive (P:C:S, 7:2:1) were labelled with ^{99}Tc^{m} on the lipid membrane, and their *in vivo* distribution studied in normal rats and in two rat tumour models. Wistar rats bearing inguinal Walker 256 carcinomas received intravenous liposomes. Negative liposomes localized appreciably in the tumours (1–2% dose per gram at 24 hours) and the tumours could be demonstrated by scintigraphy. Positive liposomes showed marginally lower tumour uptake while the tumour uptake of neutral liposomes was negligible. Small liposomes were better localized than large liposomes.

Rats bearing Rd/3 tumours in a foot pad with regional lymph node metastases received liposomes by interstitial injection close to the primary tumour. Normal rats were similarly injected in a foot pad. At five hours there was uptake of radioactivity in the lymph nodes which could be clearly seen scintigraphically. Positive and negative liposomes gave uptake in the primary lymph node of about 1% and 0.3% of the dose respectively. This was not significantly altered by the presence of secondary tumour. Neutral liposomes showed marked reduction in uptake in the presence of metastases.

Technetium-labelled liposomes were given by intravenous injection to twelve patients with advanced solid tumours and two patients with haematological malignancies. The liposomes concentrated predominantly in the liver and bone marrow in all cases except one of polycythemia rubra vera which was remarkable in that bone marrow uptake was not associated with liver accumulation. Only one case (a hepatoma) showed detectable radioactivity in the tumour.

Common human tumours clearly differ significantly from the rapidly growing experimental rat tumours. This suggests that even when liposome composition has been optimized, uptake of liposomes will vary with tumour type, rate of growth and any previous treatment. We see no likelihood of liposomes becoming an effective tumour-seeking radiopharmaceutical unless they can be directed specifically, perhaps by the incorporation of anti-tumour antibodies into their structure.

NEW LAMPS FOR OLD–A RE-EVALUATION OF SOME FAILED ADRENAL IMAGING AGENTS

By G. S. Boyd and M. V. Merrick

Departments of Biochemistry and Medicine University of Edinburgh

The only significant pathway of excretion of cholesterol and its metabolites is via the liver into the bile. Bile contains both cholesterol and its major metabolites, the bile acids. Neither the cholesterol nor the bile acids are present principally as waste products, but have essential roles in the absorption of food. Absorption of bile acids may be partially by passive diffusion, but is thought to be principally mediated by an active transport mechanism present only in the ileum.

The labelled cholesterol analogues used for adrenal cortical imaging also appear in the bile partly as the alcohol and partly after conversion into bile acids. The rate-limiting step in the conversion of cholesterol into bile acids is hydroxylation of the 7-position. A selenomethyl group in the 19- or the 6-position gives a compound which is hydroxylated relatively slowly, so that the biosynthesis of bile acids from 19-methyl (or 6-methyl) selenomethylcholesterol is inefficient. Chemical synthesis of ring-labelled bile acids proved difficult and we have therefore investigated four compounds with labels in the side chain, namely 23-selena $3\alpha7\alpha$ chenodesoxycholic acid, 22-selena cholic acid (22 SC) 23-selena 25-homodesoxycholic acid and 23-selena 25-homocholic acid (23, 25 SH). As well as the acids, glycine and taurine conjugates of 22 SC and the taurine conjugate of (23, 25 SH) were investigated.

The compounds were evaluated in rats with biliary fistulae. A mixture of one of the test compounds with ^{14}C labelled cholic acid was administered via an oro-duodenal tube. The rate of appearance of ^{14}C and ^{75}Se in the bile was measured and the ratio of the two compared with that in the original mixture. Three of the compounds were found to have ratios close to unity and these are being investigated further.

TECHNETIUM 99M RADIOPHARMACEUTICAL KITS–IN-HOUSE OR COMMERCIAL?

By A. M. Millar

Royal Infirmary, Edinburgh

The role of the in-house technetium 99m radiopharmaceutical kit is examined using two in-house kits currently in use in Edinburgh as examples. The preparation, labelling and quality control of these kits is described.

Reprints of these abstracts may be obtained free from the Managing Editor, THE BRITISH JOURNAL OF RADIOLOGY, 32 Welbeck Street, London W1M 7PG (01-935 6867).

* P = phosphatidylcholine; C = cholesterol; S = stearylamine; D = dicetylphosphate.

The first, the bone-imaging agent methylene diphosphonate has been prepared as a freeze-dried kit since 1976. The radiochemical purity of the labelled kit is consistently greater than 98%. This kit is still manufactured in-house although commercial kits have since become available, because it can be prepared much more cheaply than equivalent commercial kits.

The second is a kit for the labelling of human serum albumin by an electrolytic process. The blood retention of this preparation is compared with that of four commercial kits where the ^{99}Tc^{m} is labelled to the albumin by reduction with stannous chloride. These stannous-reduced preparations have a typical blood clearance of 30–40% in 30 minutes while the electrolytic kit shows only 5–10% clearance over the same time.

The following factors must be considered when undertaking the preparation of an in-house kit: (1) the efficacy of the resulting radiopharmaceutical—this may be greater than commercial equivalents; (2) the facilities available for manufacture; (3) the quality-control facilities available; (4) the cost; (5) the ease of preparation.

LUNG UPTAKE OF LIVER SCANNING AGENTS

By T. McCarthy

New Addenbrooke's Hospital, Cambridge

Lung uptake of radio-labelled colloids, as a result of both pharmaceutical and clinical factors, has been reported in the literature. In Cambridge a scheme for recording defective products and unusual organ distributions of radiopharmaceuticals was established in 1975 to correlate all such findings and thereby better attempt to ascertain their cause. A survey of these reports over the past three years indicated that labelled colloids are one group of radiopharmaceuticals which have given rise to problems and possible reasons for these are discussed.

The ease with which radio-labelled colloid can be prepared from kits belies the underlying complexity of the formulations being handled. As a result many investigators are unaware of factors which might alter the size and hence distribution of the colloid when administered to the patient. Apart from the well documented effect of aluminium ions on colloid size, a number of other factors are considered including different sorts of rubber closures, disinfectants and stabilizing agents. Different methods for the determination of particle size are also compared and evaluated.

The proposed mechanism of uptake of colloids by cells of the reticuloendothelial system is reviewed and a number of clinical situations which have been associated with lung uptake are discussed. The pathological conditions which have been proposed to account for lung uptake are discussed and evaluated in the light of the author's own experience. These include: increased phagocytic activity in the pulmonary capillaries, adherence of colloid particles to altered endothelium in pulmonary capillaries and altered immunological state.

THE COMPARATIVE PHARMACOLOGY OF TECHNETIUM IDA DERIVATIVES

By P. H. Cox

Rotterdamsch Radio-Therapeutisch Instituut
Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

The precise mechanism by which technetium-labelled IDA derivatives are accumulated in hepatocytes and excreted into the bile has not been established. It is difficult to identify whether these materials are excreted unaltered into the bile because, when mixed with fresh bile they immediately bind to one or more bile salts.

A number of claims have been made about the relative efficiency of different derivatives which are primarily based on differences in turnover and excretion rates. In the study reported here a number of technetium IDA derivatives which have been used in clinical studies have been examined using an animal model.

It can be concluded that the differences in rates of accumulation in the hepatocytes and excretion into the bile are primarily due to differences in the molecular size of the complexes but that otherwise the patterns are qualitatively the same.

THE PRODUCTION OF IODINE 123

By J. G. Cuninghame

Chemistry Division, AERE, Harwell

In general, radionuclides can be produced by irradiation in reactors which results in neutron-excessive nuclides decaying by β^- emission, or in particle accelerators leading to neutron-deficient nuclides which decay by β^+–emission, electron capture, or a mixture of the two.

^{123}I is a neutron-deficient, cyclotron-produced nuclide made broadly by one of two routes:

(a) direct, in which the product of the reaction is ^{123}I itself, or

(b) Indirect, in which the product is ^{123}Xe which decays by β^+–emission to ^{123}I.

We use the second of these because product purity is better and, in particular, ^{124}I contamination is impossible since ^{124}Xe is stable.

We use the nuclear reaction

$$^{127}\mathrm{I}(p,5n)\ ^{123}\mathrm{Xe}\rightarrow{}^{123}\mathrm{I}$$

Our target ^{127}I is in the form of the dense organic liquid CH_2I_2. Our yield is high at about 10 mCi/μAh and our final product is sterile, contains no pyrogens, contains no other radioactive nuclides except $<0.2\%$ ^{125}I (at time of despatch) and is $>95\%$ I^-.

We have so far sent out 16 batches to the French Atomic Energy Commission and 21 to DHSS hospitals on a 44 week trial sponsored by the DHSS. Continuance of supply at the end of the trial is dependent on there being sufficient orders to make the work commercially viable.

CLINICAL PRACTICE WITH IODINE 123

K. E. Britton, C. C. Nimmon, A. Fountos,
B. Shapiro, S. Londres and A. T. Elliott

Department of Nuclear Medicine, St. Bartholomew's Hospital
London EC1

The tradition of using iodine in nuclear medicine was built upon a fundamental concern for measuring function by making the best use of the physiology of the organ of interest. The availability of ^{123}I enables improved imaging with compounds of established physiological pedigree as, for example, with bromosulphalein (BSP) and orthoiodohippurate (OIH), introduced in 1925 and 1933 respectively. The wealth of experience gained with these agents in animals, birds and man gives a fully knowledgable basis to their use as function tests. This is not true for most technetium labelled compounds.

Previous results of static imaging in 65 patients with ^{123}I BSP showed seven patients in whom the ^{99}Tc^{m} sulphur colloid scan gave a result that conflicted with that from BSP and in each case the interpretation of the BSP scan was the relevant one. The main advantages of BSP over ^{99}Tc^{m} cholographic agents are its longer residence time in the liver allowing multiple static liver imaging and its renal excretion of less than 2% in the presence of jaundice. The ^{99}Tc^{m} cholographic agents show about 15% renal excretion even in the normal and much higher levels in jaundice.

We have switched all our routine renal pre- and post-operative evaluation to ^{123}I OIH in preference to glomerular filtered technetium agents, since the uptake efficiency of 5 to 1 in favour of OIH is an important way of decreasing background and improving quantitation. Individual renal function over 10% of total favours restorative surgery, an important management decision in urology.

We have shown that ^{123}I has specific advantages for thyroid imaging in three contexts: in ectopic thyroid tissue where the pertechnetate blood pool may interfere; in thyroid cancer; and in the situation where the pertechnetate scan shows a "hot" spot without suppression of the rest of the gland. In this last context, the ^{123}I image is often normal. We have used fatty acids, the basic substrate for the heart, labelled with ^{123}I for studying myocardial metabolism. The left ventricular muscle wall images obtained are as good as or better than thallium 201 images due to the better energy characteristics of ^{123}I. Unfortunately the technique of labelling is still of variable efficiency.

The great advance with ^{123}I lies in its future use as a protein label, an area where ^{99}Tc^{m} labelling has so often been disappointing. The labelling of fibrinogen or plasmin for clot detection and the labelling of protein antigens and antibodies, such as anticarcinoembryogenic anti-tumour and anti-protozoal localizing agents, will follow. The use of labelled protein hormones to identify receptor binding and the development of dynamic tests, *e.g.* with ^{123}I T3 or ^{123}I ADH, builds on the knowledge gained *in vitro* with ^{125}I labelling for radioassays. The use of ^{123}I antipyrine for brain and lung-water measurement and ^{123}I cholesterol, metyrapol and aminoglutethimide adrenal agents has already been reported. The reduction in radiation hazard by an order of magnitude over ^{131}I, the great experience in labelling with iodine and the physical characteristics of ^{123}I are positive advantages for the future.

PHARMACEUTICAL EXPERIENCE WITH IODINE 123

By L. A. Hawkins, L. J. Dyke and A. T. Elliott

Department of Nuclear Medicine, St. Bartholomew's Hospital
London EC1

The physical characteristics of ^{123}I place this nuclide second only to ^{99}Tc^{m} as a potentially useful radionuclide in nuclear medicine procedures. As part of a one year trial of the material obtained from the UKAEA Harwell, we are producing several radiopharmaceuticals in our department whilst carrying out a clinical trial of their diagnostic value compared with ^{99}Tc^{m} compounds. As iodide, with adjustment of pH to 6.0, we have studied 55 patients with ^{123}I and ^{99}Tc^{m} as pertechnetate referred for thyroid scans. For dynamic kidney function studies with the gamma camera we have, together with four other UK hospitals, developed a rapid procedure for labelling o-iodo-hippuric acid with an efficiency and radiochemical purity greater than 95%. This is compared with the widely used ^{99}Tc^{m} DTPA.

For liver scanning ^{123}I-bromosulphalein has been synthesized with an efficiency of 90% and we are in the process of comparing this liver cell agent with the ^{99}Tc^{m} HIDA complexes. Less success has been achieved with ^{123}I-hexadecanoic acid for myocardial infarct detection as labelling yields are poor and variable, but we hope to improve these and obtain further clinical results.

IODINE 123 IN THE INVESTIGATION OF RENAL DISEASE

By H. J. Testa

Department of Nuclear Medicine
Manchester Royal Infirmary, Manchester

^{123}I-hippuran has been used to study renal function in a selected group of patients with a variety of renal pathologies. All patients were injected intravenously with 15 μCi per kg bodyweight while sitting in front of a gamma camera linked to a minicomputer system. Frames were stored at intervals of 20 seconds for periods of 20 to 40 minutes. In patients with suspected obstruction a diuretic was given (0.5 mg per kg bodyweight of Frusemide) (O'Reilly *et al.*, 1979) at 20 minutes after the start of the test.

In the analysis of each case relative renal function was estimated, and activity-time curves were derived for areas of interest over the whole kidney, parenchyma, pelvis, ureter, bladder and a mid-line background region. Blood background subtraction and deconvolution studies were carried out where appropriate.

This test is particularly useful in the evaluation of patients with poor renal function, suspected upper urinary tract obstruction, lower ureteric obstruction and duplex kidneys in which it is possible to establish the function of each moiety.

Because of the low radiation dose associated with the use of ^{123}I-hippuran this radiopharmaceutical is recommended for the evaluation of renal disease in patients of all ages.

REFERENCE

O'Reilly, P. H., Shields, R. A. and Testa, H. J., 1979; (Eds.) in *Nuclear Medicine in Urology and Nephrology* (Butterworths).

IODINE 123-IODODEOXYURIDINE: A POTENTIAL INDICATOR OF TUMOUR RESPONSE TO TREATMENT?

By A. B. Robins and D. M. Taylor

Radiopharmacology Department, Institute of Cancer Research
Sutton SM2 5PT

The management of human cancer would be aided considerably by the development of a quantitative *in vivo* technique for monitoring the response of tumours to radio- or chemotherapy. One approach to this problem is to use a gamma ray emitting DNA precursor, such as ^{123}I-iododeoxyuridine, in conjunction with quantitative scanning techniques. For such a technique to yield meaningful results it is essential that the total uptake of the precursor in the tumour should be directly related to the rate of cell proliferation. The objective of this study was to measure the proportion of the administered precursor which was incorporated into the DNA of treated and untreated tumours.

Studies were carried out in Balb/c mice bearing the ADJ/PC6 plasmacytoma which were given ^{125}I-iododeoxyuridine and ^{14}C-thymidine. The distribution of radioactivity in the DNA, RNA, protein and acid-soluble pools were measured at various times after radiopharmaceutical administration. In untreated tumours 90% of the ^{14}C and 70% of the ^{125}I was associated with the DNA fraction within four hours of administration. However, when the precursors were administered 24 hours after treatment with cyclophosphamide (200 mg/kg) the total uptake of both precursors decreased markedly and the uptake into DNA was slower. For ^{125}I-iododeoxyuridine the uptake into DNA was 50% of the total radioactivity at 24 hours, but only 10% was present in the acid soluble pool at this time.

It is concluded that there is a strong possibility of using ^{123}I-labelled iododeoxyuridine, combined with quantitative scanning techniques, for assessing the response of some human tumours to treatment. Further experimental work is needed to determine the optimum times for scanning after radiopharmaceutical administration.

Book review

Sources and Effects of Ionizing Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation. 1977 Report to the General Assembly, with Annexes. (United Nations, New York), 1977. pp. 725, $28.00.

Since 1958 the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has published seven reports of which this one was issued in 1977. The previous report appeared in 1972.

Like its predecessors this latest report contains an immense body of data, a lot of it in tabular form, which makes it an essential source of information for a wide audience interested in the effects of ionizing radiations on man and animals.

About half of the report deals with sources and levels of radiation exposure in the environment and the latter are updated from the estimates provided in 1972. Interestingly, the latest figures for doses from natural terrestrial sources have been reduced by about 30%. This substantial change is a result of better information on the doses derived from these sources. On the other hand, revised estimates for the exposure of red bone marrow to ^{40}K show that there is an increase by almost a factor of two in the dose delivered to this tissue compared with the assessment made in 1972. In the four years since the last report a further 20 nuclear explosions in the atmosphere have resulted in a 2% increase in dose commitment in the northern hemisphere and 6% in the southern hemisphere. It is estimated that exposure arising from the use of nuclear power contributes less than 1% of the dose received from natural sources. Despite a 5–15% annual increase in the diagnostic uses of radiations in the technically developed countries the exposure dose has remained at about 20% of that of the natural background.

As in 1972, extensive coverage is given to genetic effects of ionizing radiations and the induction of cancer in experimental animals and in man. Also included is a section on radiation-induced effects on the different stages of mammalian development *in utero*. This last aspect has not been comprehensively reviewed by UNSCEAR since 1960.

An important aspect in the production of genetic damage is the effectiveness of irradiation at very low dose rates. Data for mouse spermatogonia suggest that mutation frequency tends to increase when the dose rate of low LET radiation is reduced below 0.8 R/min. However, this trend does not appear to be statistically significant and more data are required to be certain about it. Revised estimates are given for the rate of mutation induction for various end points of genetic damage in the mouse and in children born to survivors at Hiroshima and Nagasaki. The doubling dose for both sexes in man is probably not less than 100 rad.

The most important biological effect of low doses of ionizing radiations as a hazard is induction of cancer. A large body of new information on carcinogenesis in man is given in one of the appendices to the report. Most of this is based on exposure to relatively high doses, and it is clear that much more data are required on the effects of low doses and on the influence of dose rate on induction frequency.

Most of the available data concerning embryonic and fetal malformations induced by irradiation *in utero* have been derived from animal experiments. Although the types of injury at comparable stages of development appear to be similar in laboratory animals and in man, it is hazardous to apply data for one to the other. Human data are too few, for example, to resolve the important question of whether or not there is a threshold dose for man below which little or no teratogenic damage is caused, but the experimental evidence tends to exclude its existence.

Because of the large number of papers cited it would be surprising if errors of fact and in the interpretation of the authors' conclusions did not creep into the report. Certainly some do exist but these do not detract from the usefulness of this volume which is probably the most comprehensive source of information on the topics which it covers. The suggestions put forward at the end of each section for future research should be very helpful to workers in the field.

N. E. GILLIES.

Erratum

It has been brought to our attention that the legends to figures 6 and 7 on the article "Lymphography in angio-immunoblastic lymphadenopathy" by J. N. Bruneton *et al.* on page 114, *British Journal of Radiology, vol 52,* have been transposed.

We apologize for this error.

Forthcoming events

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of the penultimate month preceding publication (*i.e.* April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

QUANTITATION OF TUMOUR RESPONSE: A CRITICAL APPRAISAL

The L.H. Gray Conference will be held in Cambridge, England, during the week of September 10–14, 1979. The topics of the meeting are intended to stimulate a critical appraisal of the techniques that are currently in use both experimentally and clinically for assessing tumour response after therapy. The topics will include:

In situ measurements of tumour response, including improved methods of tumour detection in clinical studies.
Factors of prognostic significance.
In vitro assays of tumours excised after treatment *in vivo*.
The choice of suitable experimental models in rodents.
The role of human tumour xenografts.
Statistical evaluation of tumour response data.
The limitations and artefacts of each assay technique.
The relationship between cell survival and the *in situ* response.

Further information from Dr. J. Denekamp, Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex, England.

NON-OBSTETRIC REAL-TIME ULTRASOUND

An evening meeting, organized by The British Institute of Radiology, to be held on October 18, 1979.

Further details from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

DIAGNOSTIC IMAGING IN EUROPE

A two-day international future-orientated conference to be held October 22–23, 1979 at the Brussels Hilton, will look at new developments in the main diagnostic imaging techniques. Leading scientists and experts in their respective fields will present concise market-orientated papers.

Brochures available from the Organizers: Robert S. First Inc., 19a Avenue Marnix, 1050 Brussels, Belgium. Telephone (02) 512 5063. Telex 22859.

DISEASE OF THE COLON AND RECTUM

A day course in radiology to be held on November 6, 1979 and will include papers by invited speakers on barium enema techniques and bowel preparation, investigation of rectal bleeding and Chron's disease.

Invited speakers include Dr. Allison, Dr. Nolan and Dr. De Lacey.

Fee: £8 including lunch and refreshments.

For further details apply to: Dean's Secretary, St. Mark's Hospital, City Road, London EC1V 2PS.

NUCLEAR MEDICINE VERSUS THE REST

To be held on November 14, 1979, this meeting is to review the present contribution of nuclear medicine to the investigations and diagnosis of disease in the context of competing techniques. It is hoped to define the limitations of particular applications and indicate areas for potential growth. There will be three sessions including review papers covering applications in: 1. lungs and cardiovascular system; 2. GI tract and urinary system and 3. skeletal and other systems.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

PAEDIATRIC RADIOLOGY

A two-day course in diagnostic paediatric imaging will be held at the Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London WC1 on November 15–16, 1979. The main theme of this course will be the respiratory/cardiovascular system.

Further details and application forms are available from The Secretary, Department of Paediatric Radiology, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

RADIOBIOLOGY MEETINGS

The three work-in-progress meetings this year 1979/80 will be "The role of the stroma in radiation responses" on November 16, 1979, a general meeting on February 15, 1980 and "Biological effects of doses below 2 Gray" on May 19, 1980. Also, there will be an all-day meeting, with invited speakers on Saturday, December 8, 1979, "The rationale for unorthodox fractionation". All meetings willl be held in the Institute's Reid-Knox Hall. Titles and preliminary abstracts of proffered papers for the November meeting should reach Dr. J. H. Hendry, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Withington, Manchester M20 9BX, by October 8, 1979.

THE RATIONALE FOR UNORTHODOX FRACTIONATION IN RADIOTHERAPY

A meeting to be held on December 8, 1979.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

THE BRITISH MEDICAL ULTRASOUND SOCIETY
11TH ANNUAL SCIENTIFIC MEETING

To be held on December 17–18, 1979 in Edinburgh.

Authors wishing to submit contributions for consideration should send the title and 100–200 word abstract to the address below before September 15, 1979. Additional background information on the work would help in planning the programme.

Address for enquiries: Dr. W. N. McDicken, Department of Medical Physics and Medical Engineering, The Royal Infirmary, Edinburgh EH3 9YW.

COMPUTED TOMOGRAPHY IN ONCOLOGY

ESCAT 2, European Seminar on Computed Tomography in Oncology, will be held at the Excelsior Hotel, London, Heathrow from February 4–7, 1980.

The meeting will be of interest to radiologists, physicists, radiotherapists and members of related disciplines and there will be invited speakers from Europe and the USA, together with a limited number of proffered papers.

Topics include primary diagnosis; staging; therapeutic response; radiotherapy treating planning; tissue characterization.

Further information from: Dr. Janet Husband, Organizing Secretary, The Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT.

5TH INTERNATIONAL CONGRESS OF THE INTERNATIONAL RADIATION PROTECTION ASSOCIATION

Will take place in Jerusalem, Israel, March 9–14, 1980.

The scientific programme of the Congress will cover all aspects of radiation protection with emphasis on its central theme: radiation protection—a systematic approach to safety.

An interesting programme has been planned including a commercial exhibition and pre- or post-congress workshops and professional tours.

Social events and a programme for accompanying persons have been organized.

For further information: The Secretariat, 5th International Congress of IRPA., PO Box 16271, Tel Aviv, Israel.

B.I.R. ANNUAL CONGRESS 1980

The British Institute of Radiology Annual Congress will be held on April 17–18, 1980 and will include the Sylvanus Thompson Memorial Lecture, presented by Sir Richard Doll.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

SYMPOSIUM ON SPINE AND ITS CONTENTS

EAR "Symposium Vertebrologicum" (Spine and its Contents) will be held from April 23–25, 1980 in Prague, Czechoslovakia.

The subjects of this symposium will be recent advances and experiences in:

(a) Equipments and investigative methods of spine and spinal cord.
(b) Radioanatomy and physiology of spine and spinal cord.
(c) Radiodiagnosis of pathological conditions.
(d) Interventive (diapeutic) radiodiagnostic methods.

For further information contact The secretariat of "Vertebro 1980", PO Box 88, Sokolská 31, 120 26 Praha 2, Czechoslovakia.

XV INTERNATIONAL CONGRESS OF RADIOLOGY

The XV International Congress of Radiology will take place June 24–July 1, 1981 in Brussels, Belgium.

The scientific activities of the Congress as well as the scientific and technical exhibitions will take place in the Brussels Exhibition Centre.

Further information from: Secretariat ICR-81, Ave. Winston Churchill 234B-Box 16, B-1180 Brussels, Belgium.

TENTH L. H. GRAY CONFERENCE

Will be held in Oxford on July 13–16, 1981 on "biological actions of radiofrequency, microwave and ultrasonic radiations".

A conference to review and discuss past and current research on the radiobiology and biophysics of the radiations, particularly in relation to their potential therapeutic value.

Information/Chairman of Organizing Committee: Dr. C. R. Hill, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey.

Introduction to Clinical Radiology. A correlative approach to diagnostic imaging. By Richard H. Daffner, pp. ix+410, 614 illus., 1978 (C. V. Mosby Co., St. Louis; YB Medical Publishers, London) £10·28.
ISBN 0-8016-1203-9

This book is aimed at the medical student embarking on his clinical training, and provides, not a catalogue of radiological signs, but a basic methodology with which the student can interpret any radiograph. The book contains pertinent and essential information, providing references for those wishing to pursue the subject further.

The book is divided into two parts; the first is an informative summary of the types of radiographic imaging and their physical basis, coupled with an explanation of how each technique can be used to its best clinical potential. There follows a section on the uses of radiographic contrast media, including a helpful section on the diagnosis and management of the adverse reactions to such media.

Part two is involved with the application of diagnostic radiology to the clinical situation and each chapter covers a major body system. The chapters are subdivided into sections:

1. Technical considerations, including the use of special views for the elucidation of particular problems.
2. Anatomic considerations, providing a review of relevant anatomy and its alteration by disease.
3. Pathological considerations, describing pathological patterns, the response of the body to such pathology and the radiological appearances of both.
4. Case studies, added to conclude each chapter, enabling the reader to consolidate and apply the radiological methods described. This section I found particularly useful, providing a means of feedback through which I could assess my acquired understanding.

Common radiological pitfalls are illustrated throughout the text and serve as reminders to the prospective house officer.

This is a book which is easily read, and its fluent style and ample illustration make learning a pleasure. It instills into the reader a sound basis of radiological logic on which to found his interpretation of any radiograph with which he may be presented. It also encourages a critical approach to the various special investigations, many of which are at best expensive and at worst invasive and potentially dangerous. It is a highly informative book having much to offer the clinical student; it is a shame therefore that the price may prohibit individual possession.

CHARLOTTE A. WRIGHT.

Looking at the volume through the eyes of a teacher, I am happy to endorse these views of a clinical student with elective experience in radiology. It is a good book, but also illustrates the difficulties of teaching/learning radiology for those who need a firm grasp of its principles without excessive detail. As in teaching the bare bones of a foreign language, the temptation is to provide a phrase-book: "here is the pneumonia–can you direct me to the nearest abdominal tumour" etc. The rewards are immediate but short-lived. Building a scaffolding of outline knowledge which the student can later use and fill in for his own purposes is much harder. It has to be strong and light. Richard Daffner's book has a measure of these qualities, and I particularly enjoyed the quiz pages of clinico-radiological problems at the end of each chapter.

THOMAS SHERWOOD.

Obituary

A. L. Cornick, A.M.I.E.E., Hon.M.S.R., F.S.X-ray T.

"Nick", as he was affectionately known to many hundred student radiographers and many radiologists to whom he lectures on "equipment for diagnostic radiography", died peacefully at his home "Longmead", Langstone, Gwent on Friday, May 11, 1979 aged 73.

After an electrical engineering apprenticeship he joined J. Otley Rhodes as his first employee and commenced his life-long interest in X rays.

Over the years he installed and serviced both X-ray and electro-medical equipment in Wales and the West of England until taking over as managing director in 1948; it was after this date that he commenced lecturing at schools of radiography at Cardiff, Neath, Bath, Newport and Gloucester, and also lectured to D.M.R. students at Cardiff while also guiding the firm through the difficult period immediately after the National Health Act.

He remained an active director of the company after his retirement in 1971, even though he was now able to devote more time to his other interest of sailing on the Monmouthshire canal, where his forceful character had already made its mark since he acquired a cruiser many years ago.

We extend our sympathy to his widow, son and daughter-in-law and grand-daughter on their sad loss.

R. E. D. Williams.

The British Institute of Radiology Awards 1979

This year the Barclay Medal was awarded to Dr. Ian Kelsey Fry of St. Bartholomew's Hospital for his outstanding contributions to The British Journal of Radiology toward the understanding of the action of contrast media in the human body.

The Barclay Prize was awarded to Professor B. J. Cremin of Groote Schuur Hospital, South Africa for his many valuable contributions to The British Journal of Radiology in the field of paediatric radiology.

The Röntgen Prize was awarded to Dr. Juliana Denekamp of the Gray Laboratory, Mount Vernon Hospital for her many excellent contributions to The British Journal of Radiology in the field of radiobiology and its application to radiotherapy.

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Receipt of the following books is acknowledged as courtesy to the senders. These publications have been lodged in the Library of THE BRITISH INSTITUTE OF RADIOLOGY for the use of members.

High-voltage cable plug and socket connections for medical X-ray equipment, IEC Publication 526, pp. 18, 1978 (International Electrotechnical Commission), Fr.S.24.

Characteristics of anti-scatter grids used in X-ray equipment, IEC Publication 627, pp. 49, 1978 (International Electrotechnical Commission), Fr.S.69.

Stomach Cancer (*A series of Workshops on the Biology of Human Cancer. Report No. 6*). Edited by D. W. Piper, pp. viii + 138, 1978 (UICC Technical Report Series, vol.34,) Fr.S.1.60. ISBN 92-9018-634-X.

Directory of Cancer Research Information Resources, U.S.A. Department of Health, Education, and Welfare. 1979.

Guidelines for the Preparation of Radiopharmaceuticals in Hospitals

Revised 1979 Edition

Special Report No. 11

A Report of a Working Party

Numerous types of diagnostic agents labelled with radio-nuclides are now in routine use for the investigation *in vivo* of human disease. Many of these radiodiagnostic agents contain radio-nuclides of short half-life and for this and other reasons it is necessary to carry out their preparation in hospitals. Little official or other guidance concerning the basic procedures required for the safe preparation of these radiopharmaceuticals has, however, been available. For this reason, following a Seminar on 'Laboratory Facilities and Working Procedures for the Hospital Preparation of Radiopharmaceuticals' held at the Royal Marsden Hospital, Sutton, in October 1974, a working party was set up to prepare some guidelines on this subject. This document comprises the report of this working party; it is concerned not with individual recipes, but with basic principles and procedures. The Report should prove helpful to many of those concerned with the preparation and use of radiopharamceuticals, and it is expected to provoke useful comment and discussion, especially on the extent to which the procedures set down conform to the requirements of the Medicines Act (1968).

In revising the present report it has not been considered necessary to revise any of the original recommendations. However, the opportunity has been taken to amend certain sections to take account of the changes in United Kingdom legislation consequent on the implementation of Article 5(a) of the European Communities Directive (Euratom, 1976) on basic safety standards for health protection against the dangers of ionizing radiation.

Additional references have also been provided, and minor changes made, where necessary to bring the text up-to-date.

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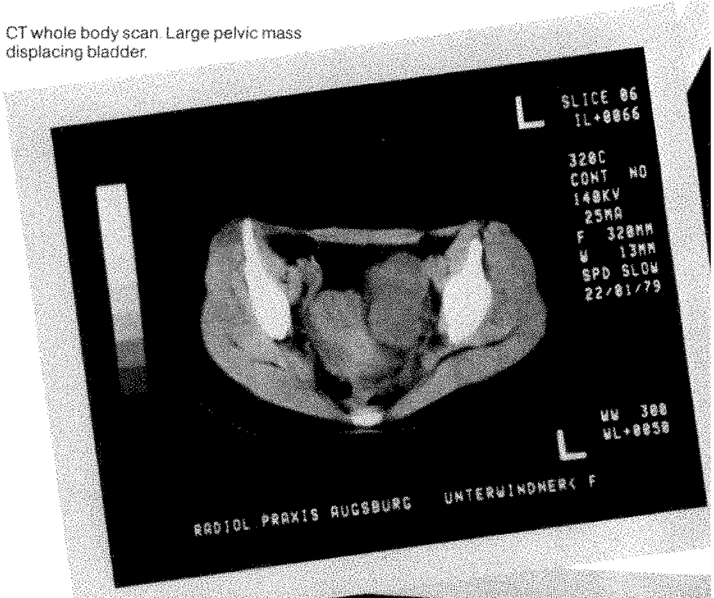

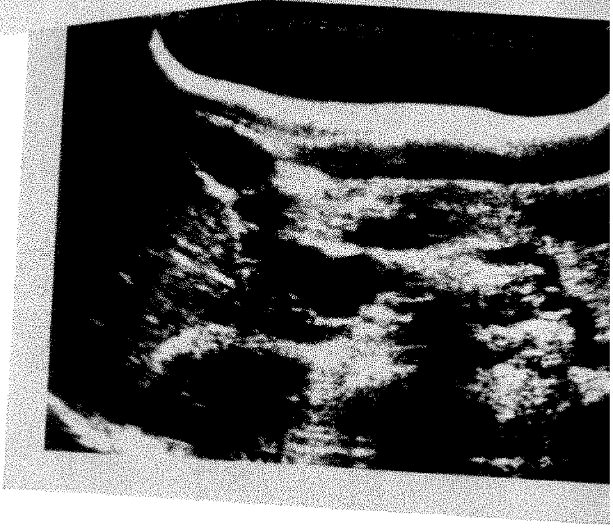

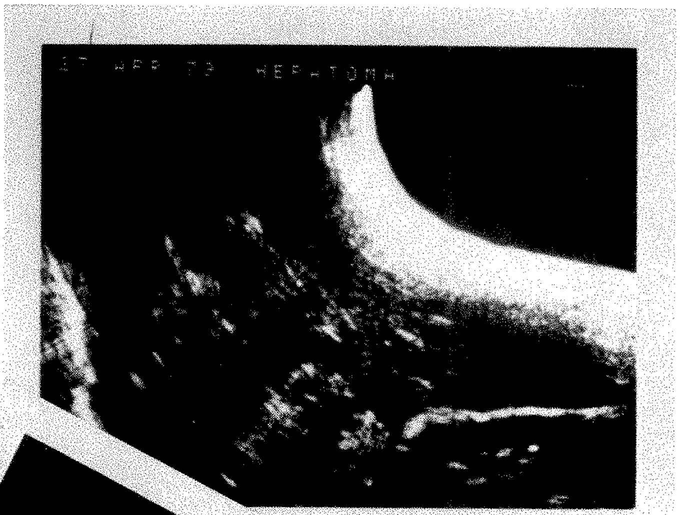

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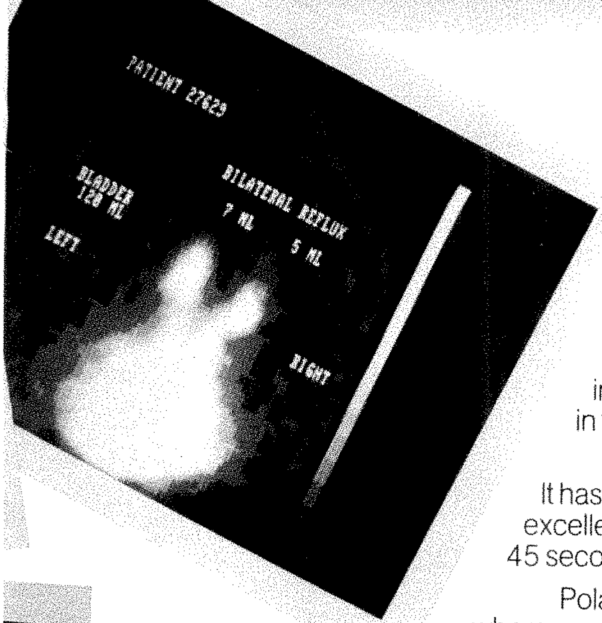

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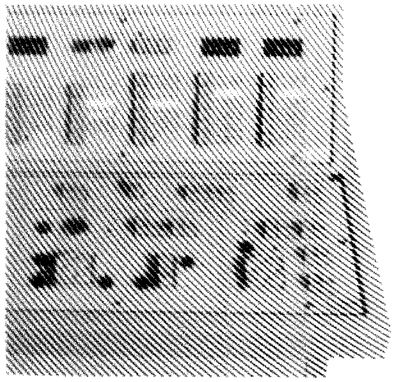

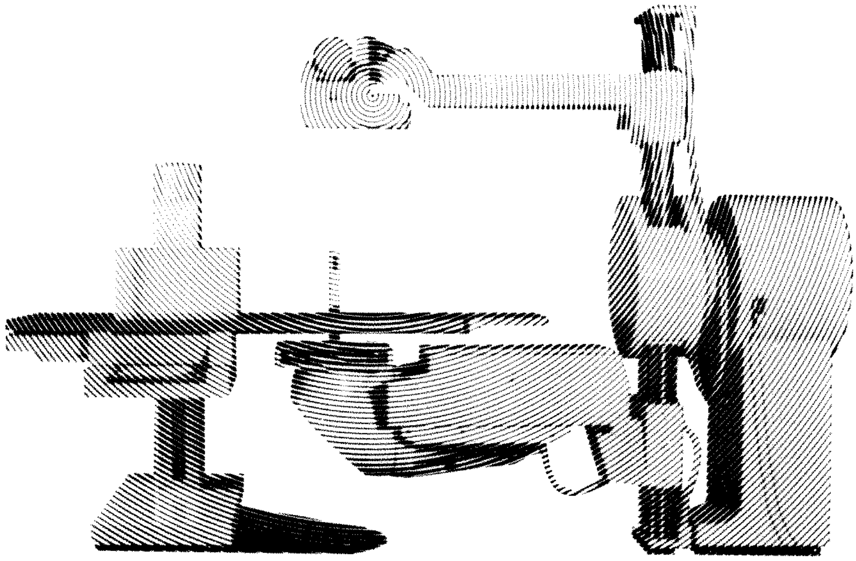

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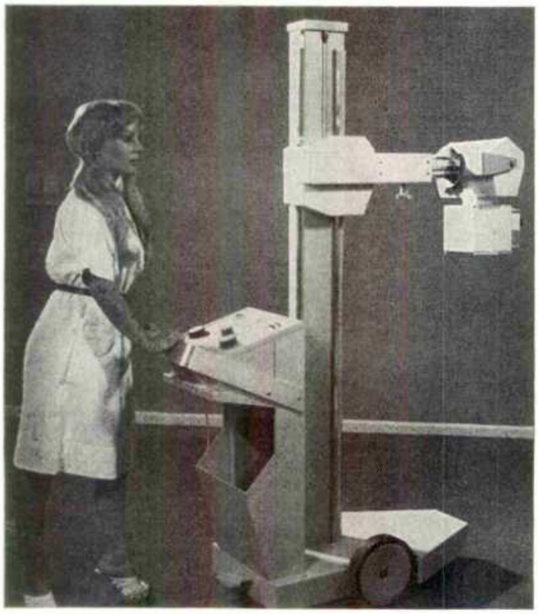

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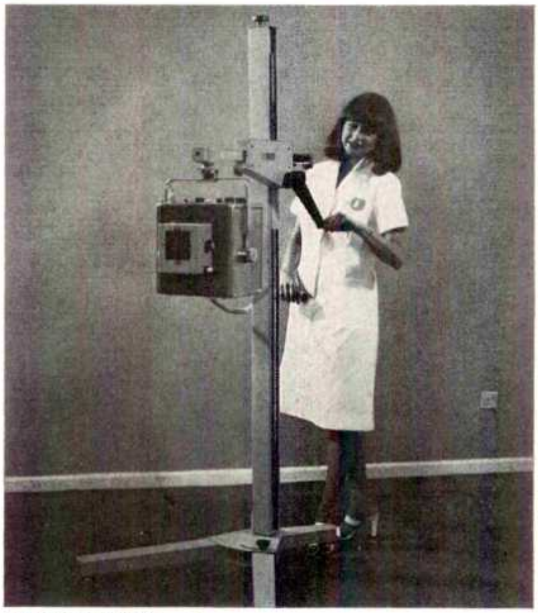

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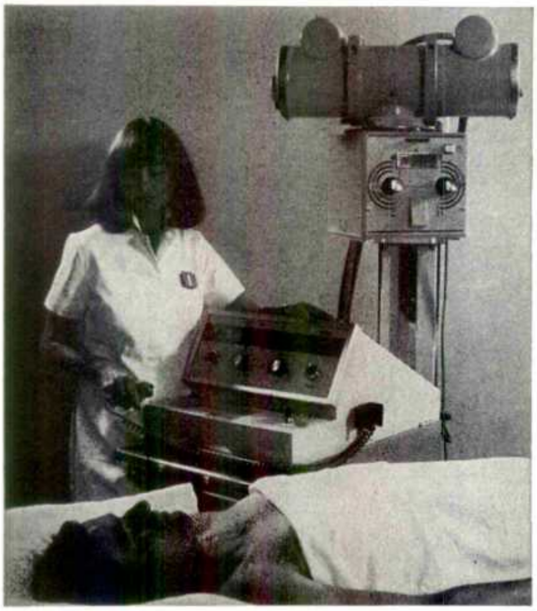

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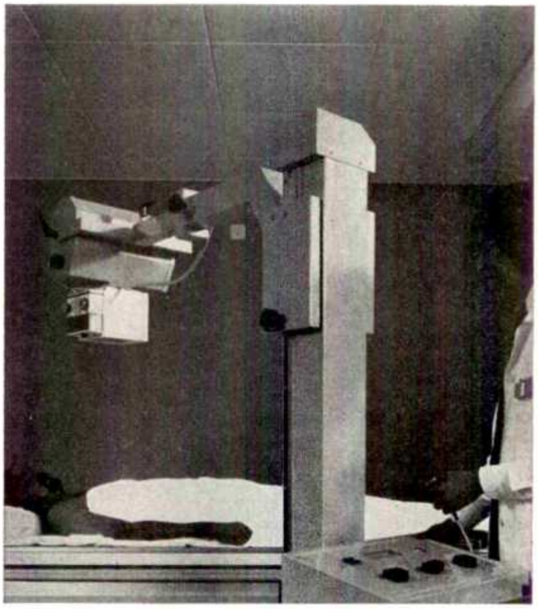

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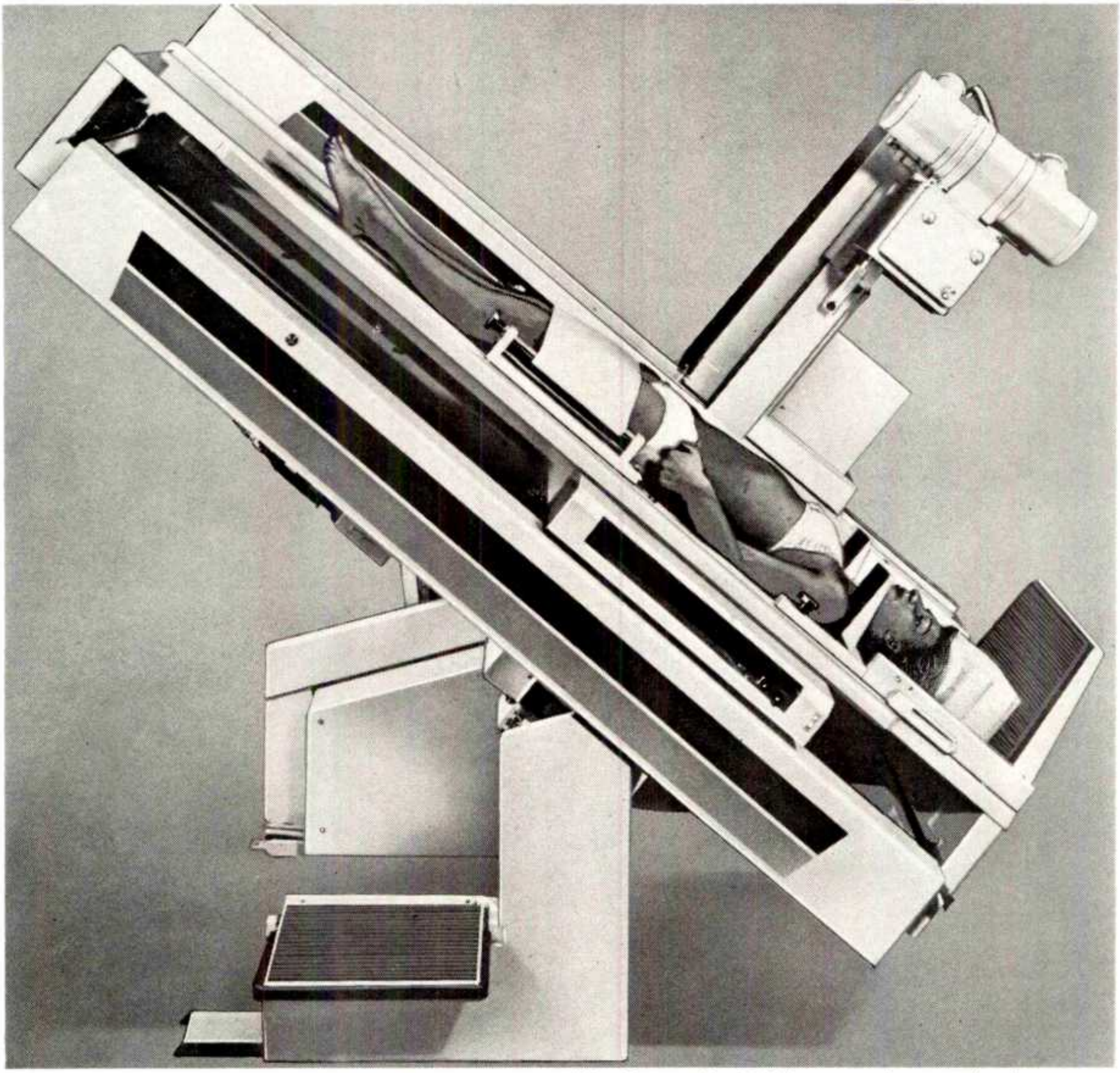

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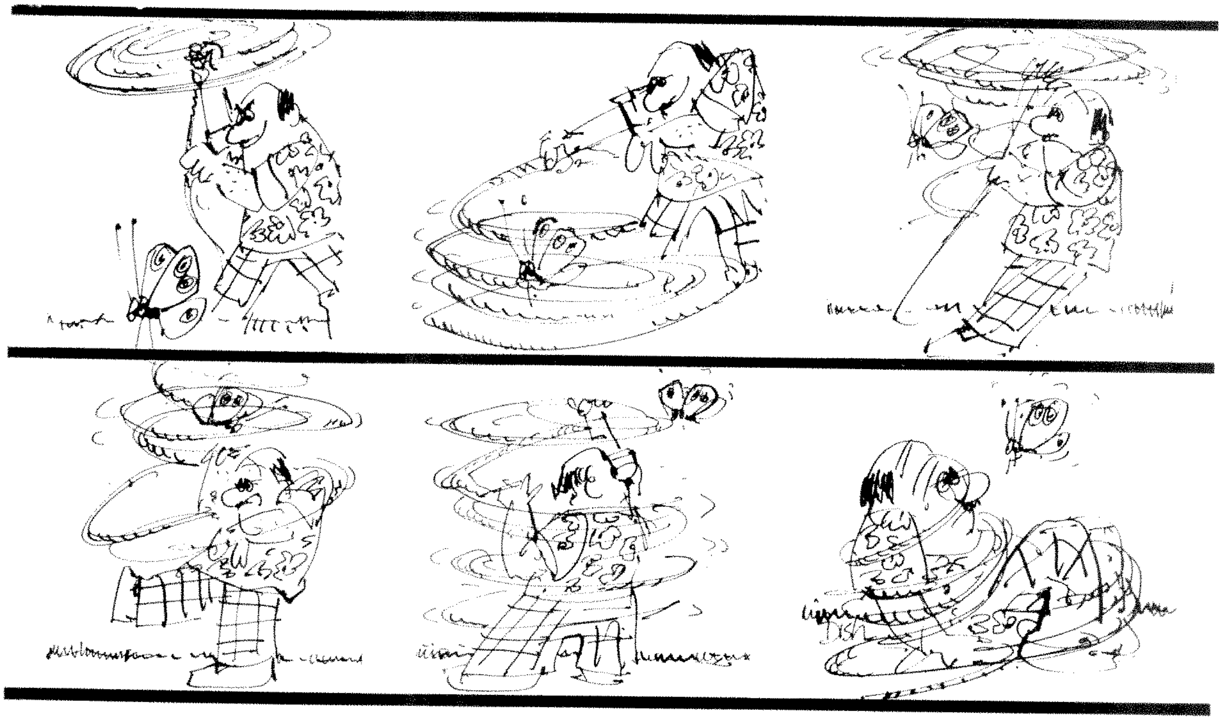

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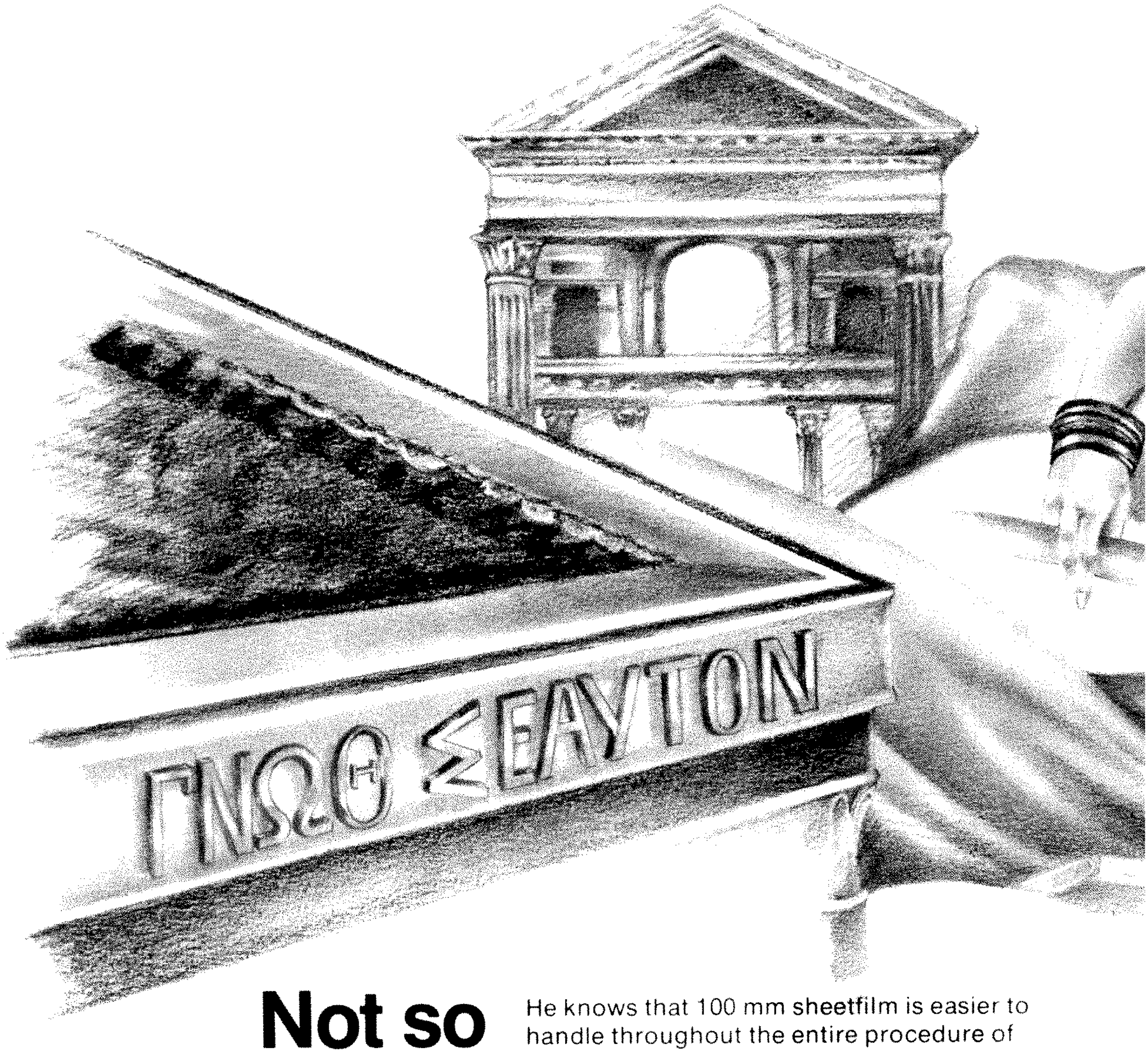

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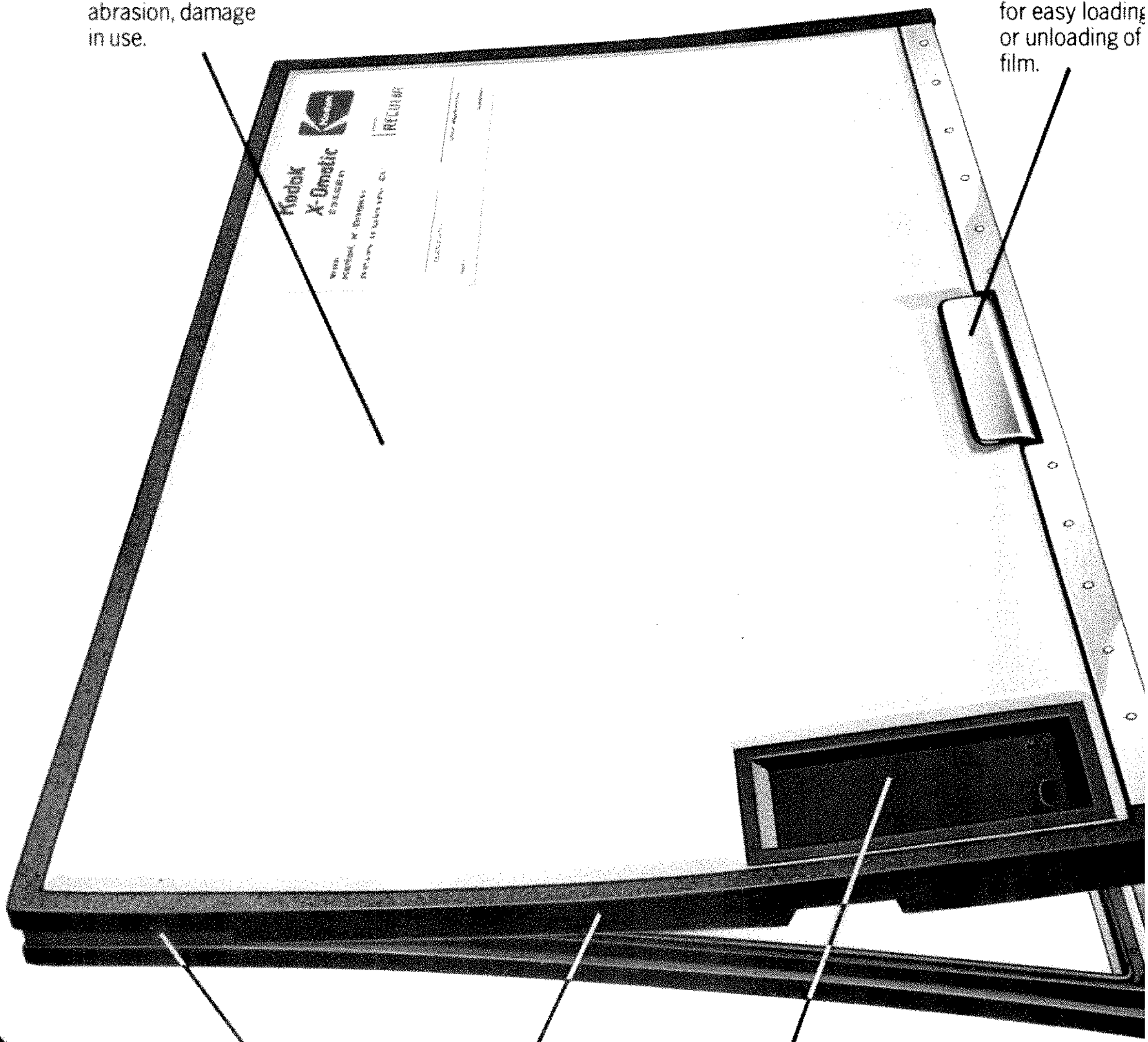

New colour coding makes service recognition uncomplicated.

Curved sides roll out air for total, uniform screen/film contact.

Patient identification window (Model C1 only) used to record patient name, time of exposure, and other essential information helps eliminate error.

Ask your Kodak Rep, "What's in it for me?"

that opened the door to roomlight handling

With the KODAK 'X-Omatic' Cassette, Kodak created a remarkable cassette for diagnostic imaging.

It could be opened with one hand. It was specially shaped to roll out air and give close screen/film contact over the whole area. And it was rugged.

Over the years, the KODAK 'X-Omatic' Cassette has been improved. But it was that initial design that made it the first cassette that can be opened, emptied, reloaded and closed entirely by a machine: the amazing KODAK 'X-Omatic' Cassette Multiloader.

The KODAK 'X-Omatic' Cassette. It's the key to more efficient radiographic imaging.

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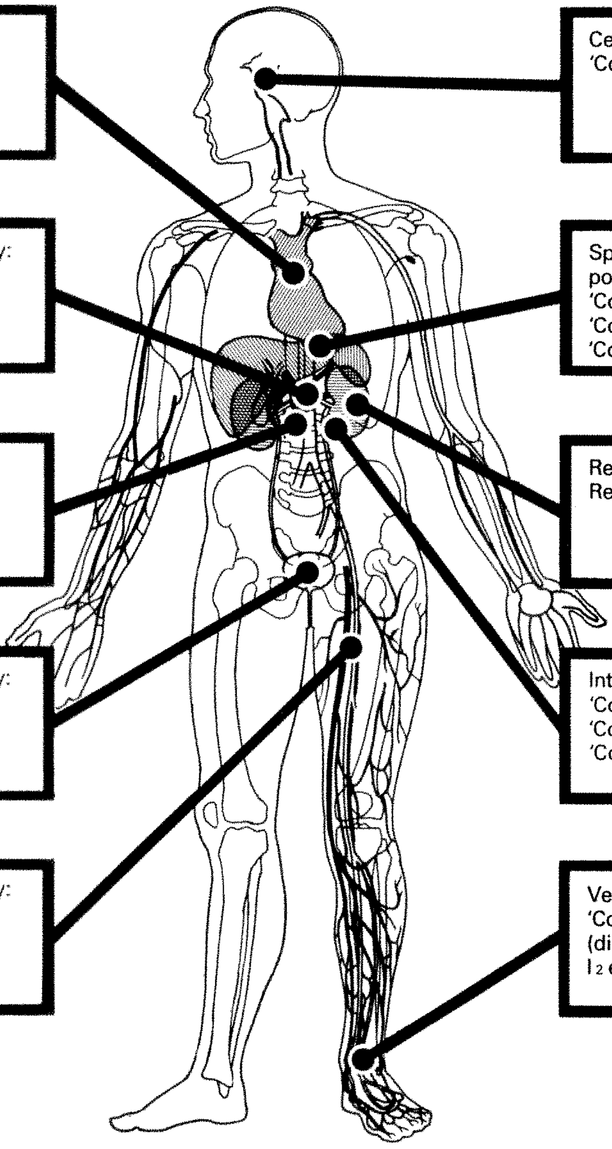

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Let us put you fully in the picture about the 'Conray' range of contrast media

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Abdominal-aortography:
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'Conray 420':
'Conray 325':
Cardio – 'Conray'

Gastroenterography:
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Retrograde cystography:
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(suitably diluted)

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(diluted to 150–200 mg I_2 equivalent)

Conray Contrast Media
(Meglumine and sodium iothalamate)

No matter what your particular requirements may be, there is almost certainly a presentation suitable. If you are in any doubt whatever, contact your May & Baker representative or telephone our Medical Information Department (01-592 3060)

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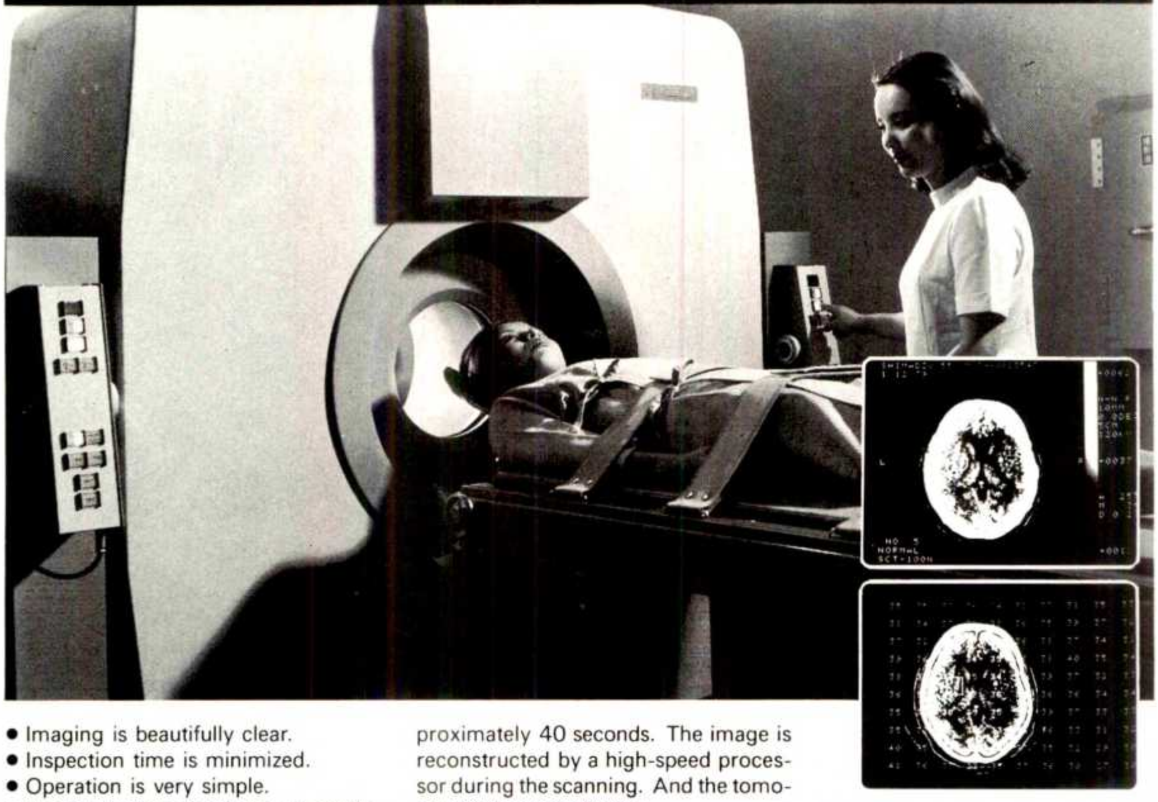
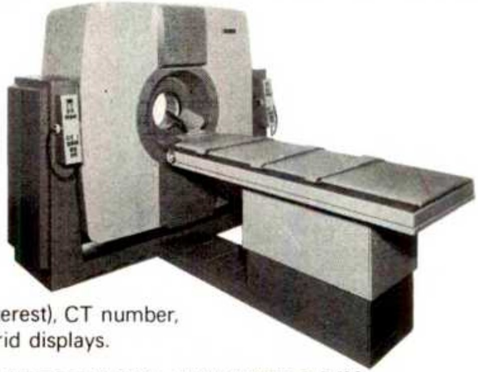
The Shimadzu SCT-100N 40-Second Rapid Scan

Computerized Axial Tomographic Scanner for Neuroradiology



- Imaging is beautifully clear.
- Inspection time is minimized.
- Operation is very simple.
- A wide variety of software is available.
- The entire system is compact.

Computerized tomography has become an essential part of neurological and emergency diagnosis procedures. And easy-to-operate equipment is especially necessary in emergency applications. The Shimadzu computerized axial tomographic scanner for neuroradiology, the SCT-100N, was developed through long engineering experience to meet just such requirements. The SCT-100N completes scanning in only approximately 40 seconds. The image is reconstructed by a high-speed processor during the scanning. And the tomographic image is displayed immediately after the scanning is completed. Image display is by means of a black and white CRT with a 64-level grey scale and 256 × 256 matrix. The main processor, a mini-computer, makes possible a wide range of practical image processing, including ROI (region of interest), CT number, blinking, enlarged and grid displays.



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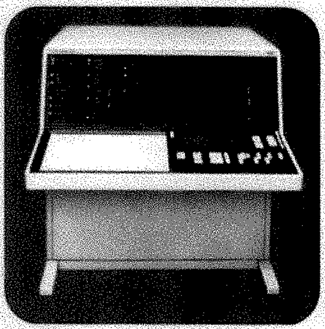
TPS extended to Brachytherapy



Next to the highly accurate teletherapy programme the TPS offers more. It also provides extensive facilities for calculation of brachytherapy plans with needles, straight and curved wires and seeds.
The 'question and answer' mode of operation makes processing easy and virtually self-explanatory.
From the many applicational advantages we just mention:
- correction for tissue absorption
- correction for oblique filtration
- automatic source decay correction
- inherent self-checking on accuracy of source positions and dimensions
- dose information geometrically related to an anatomically recognisable point

This facility is now standard on all TPS equipment.

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Building QM, Eindhoven, The Netherlands

Philips Medical Systems Ltd., Kelvin House,
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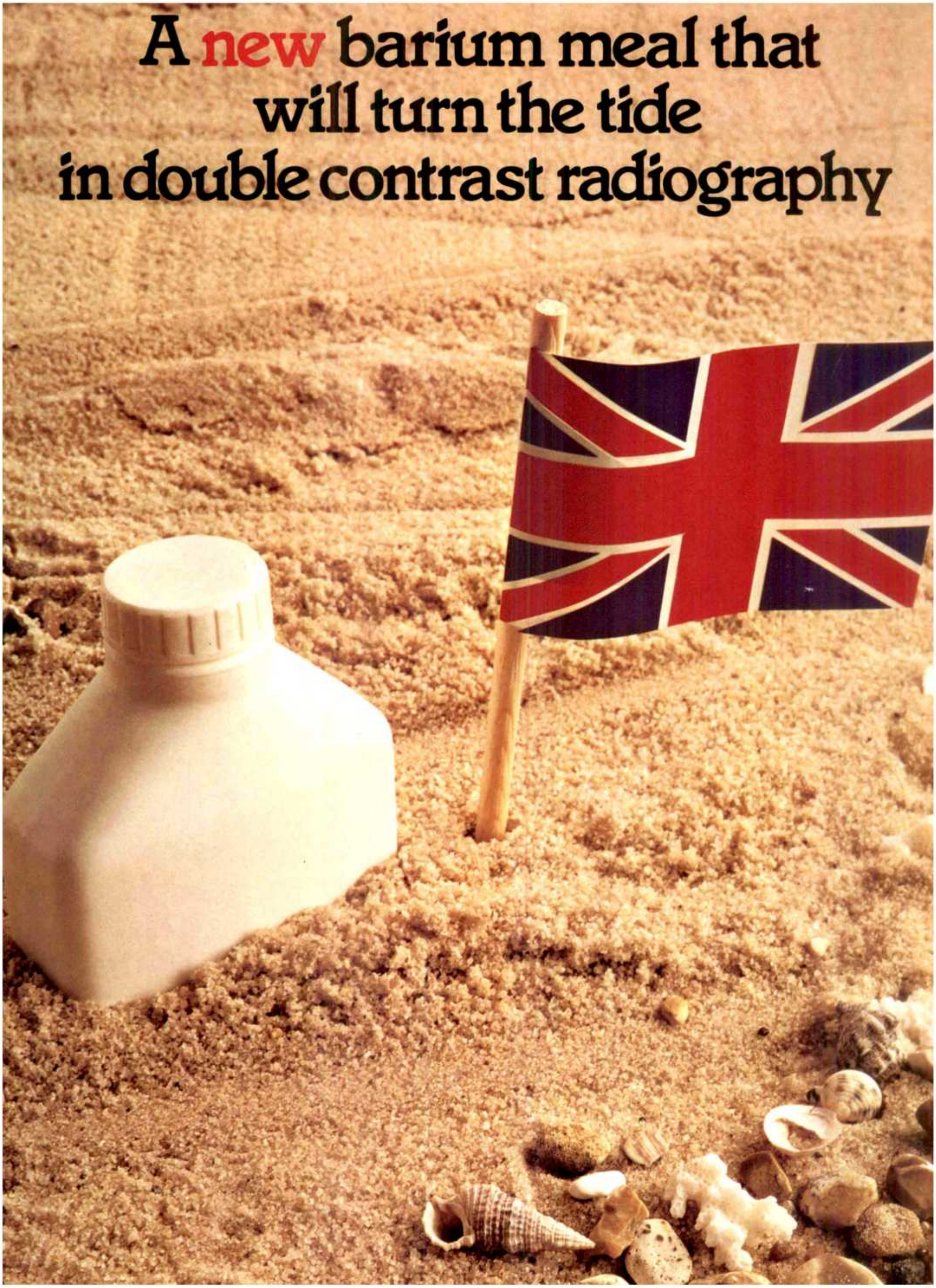


A new barium meal that will turn the tide in double contrast radiography

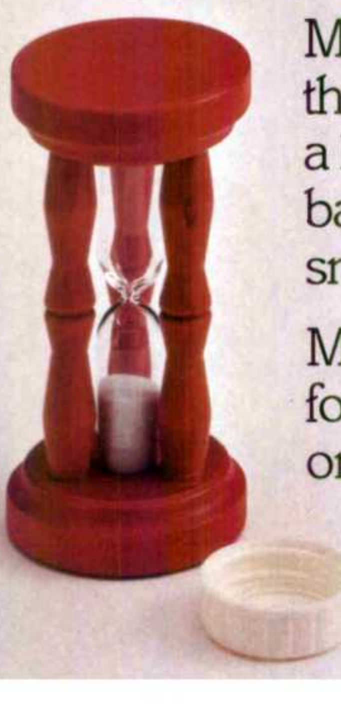
Micropaque D

(Barium Sulphate 100%w/v)

A new low viscosity barium meal for use in double contrast radiography

Micropaque DC represents a significant advance in formulation and production of barium for double contrast work. Using existing CO_2 tablets Micropaque DC provides a medium for excellent definition of detail and it only takes a minute to prepare.

All essential requirements have been built into the pack. It is light in weight, can be held in the hand easily and resealed to reduce wastage.



Micropaque DC has been formulated for the discerning Radiologist demanding a high standard of definition, from his barium contrast medium, to identify the smallest irregularities.

Micropaque DC reduces preparation time for the busy radiographer, no pre-mixing or mechanical agitating.

Micropaque DC
is ready for use in one minute.

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Micropaque DC

(Barium Sulphate 100% w/v)

Presentation
A low viscosity white suspension containing 100% w/v of barium sulphate with a bland taste and particularly suited to the Double Contrast Technique.

Uses
Radiological investigations of the gastro-intestinal tract.

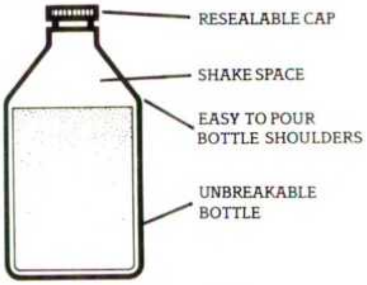
Doses and Administration
The volume of Micropaque DC used will depend on the patient, the procedure and technique involved. The following dosages represent a basic guide to the quantities suitable for routine examinations: Barium Swallow 40-60 ml undiluted. Double Contrast Stomach and Duodenum Examination 100-150 ml undiluted. Follow through small Bowel Examination 150-250 ml undiluted. Barium Enema 250-500 ml diluted with 500-1000 ml water.

Contra Indications Warnings etc.
Perforation of any region of the gastro-intestinal tract and intestinal obstruction. Pyloric stenosis might be considered as contra-indications to the use of barium sulphate.

Pharmaceutical Precautions
Shake well before use. Store at room temperature. Do not freeze. A light brown supernatant layer may appear and is quite normal. It will disappear when the bottle is shaken.

Legal Category
P

Package Quantities
300 ml plastic bottle containing 250 ml suspension and 50 ml 'shake space'. 15 bottles in each pack.



Further Information
Micropaque DC., having a high density combined with a low viscosity, has been formulated to demonstrate particularly fine definition in conjunction with a suitable effervescent distending agent for Double Contrast Technique in the gastro-intestinal tract.

Basic N.H.S. Price £1.26 for 250 ml

Product Licence Number
0838/0002

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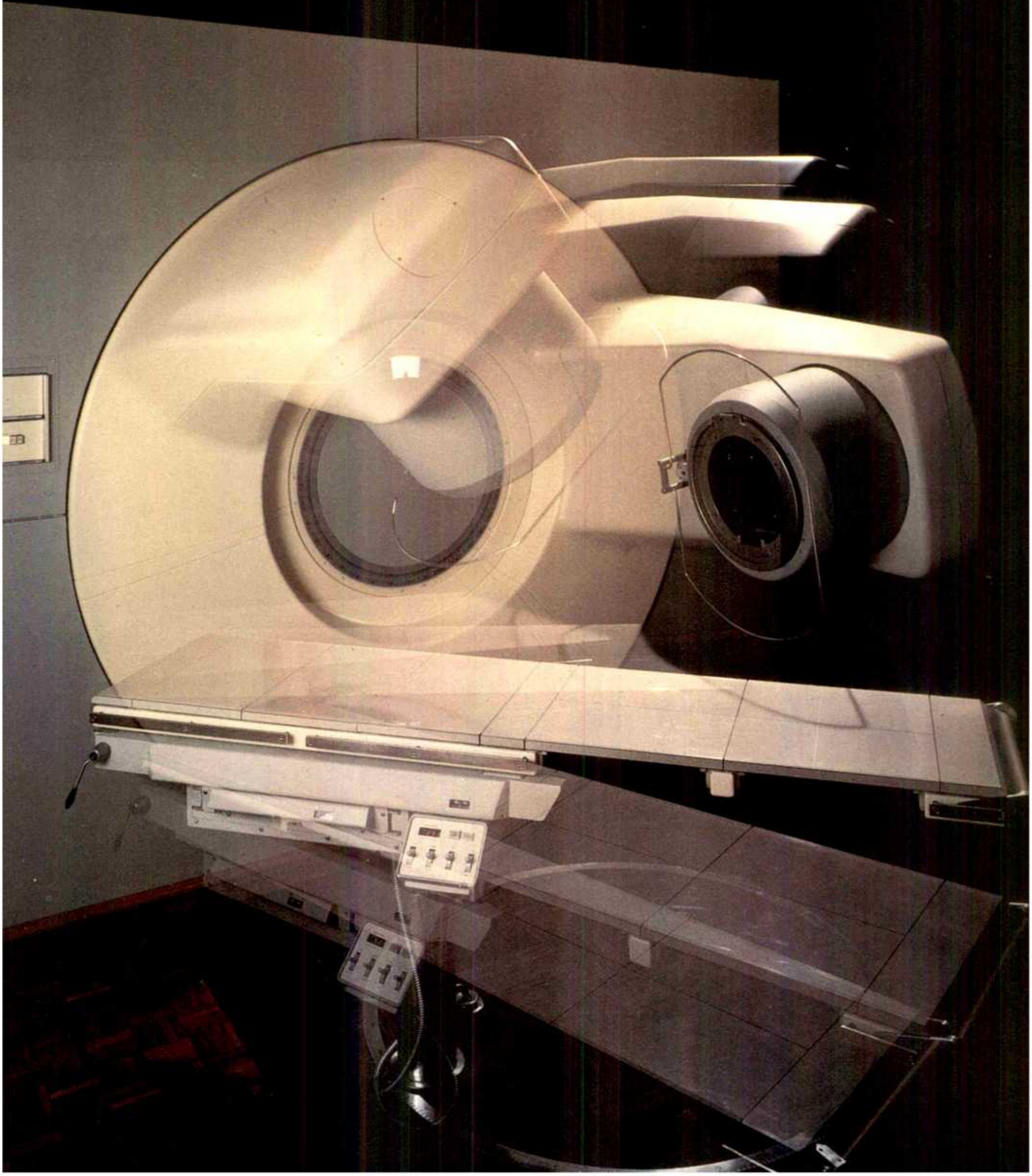
HAS THE TREATMENT CONTROL SYSTEM YOU USE
TODAY, THE TECHNOLOGY FOR THE YEAR 2000?



Philips announce the launch of an entirely new control console for SL75-14 and SL75-20 accelerators.

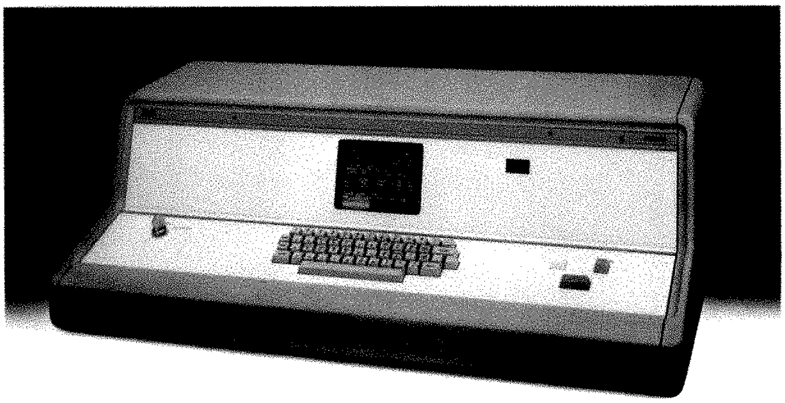
The new console gives improved control and more information shown with greater clarity than ever before.

Traditional knobs, switches and meters have been superseded by a microprocessor controlled video display unit and an alpha/numeric keyboard. Together these make treatment settings as easy as operating a pocket calculator.

The new control console is programmed to lead the operator through the setting-up procedure by information supplied on the screen. Any settings which are inconsistent with the type of treatment or with selections made inside the treatment room are highlighted on the screen and operation is inhibited until a correction has been made. The system incorporates fully independent dual channel dosimetry, a back-up timer and other safety features pioneered by Philips.

Interfaces are available to connect the new control console to the Philips Vericord automatic treatment verification and recording equipment and to external computers for further automation.

Contact Philips at one of the addresses shown below for more information on new developments in radiation therapy equipment.



Together, we can build for the future today.

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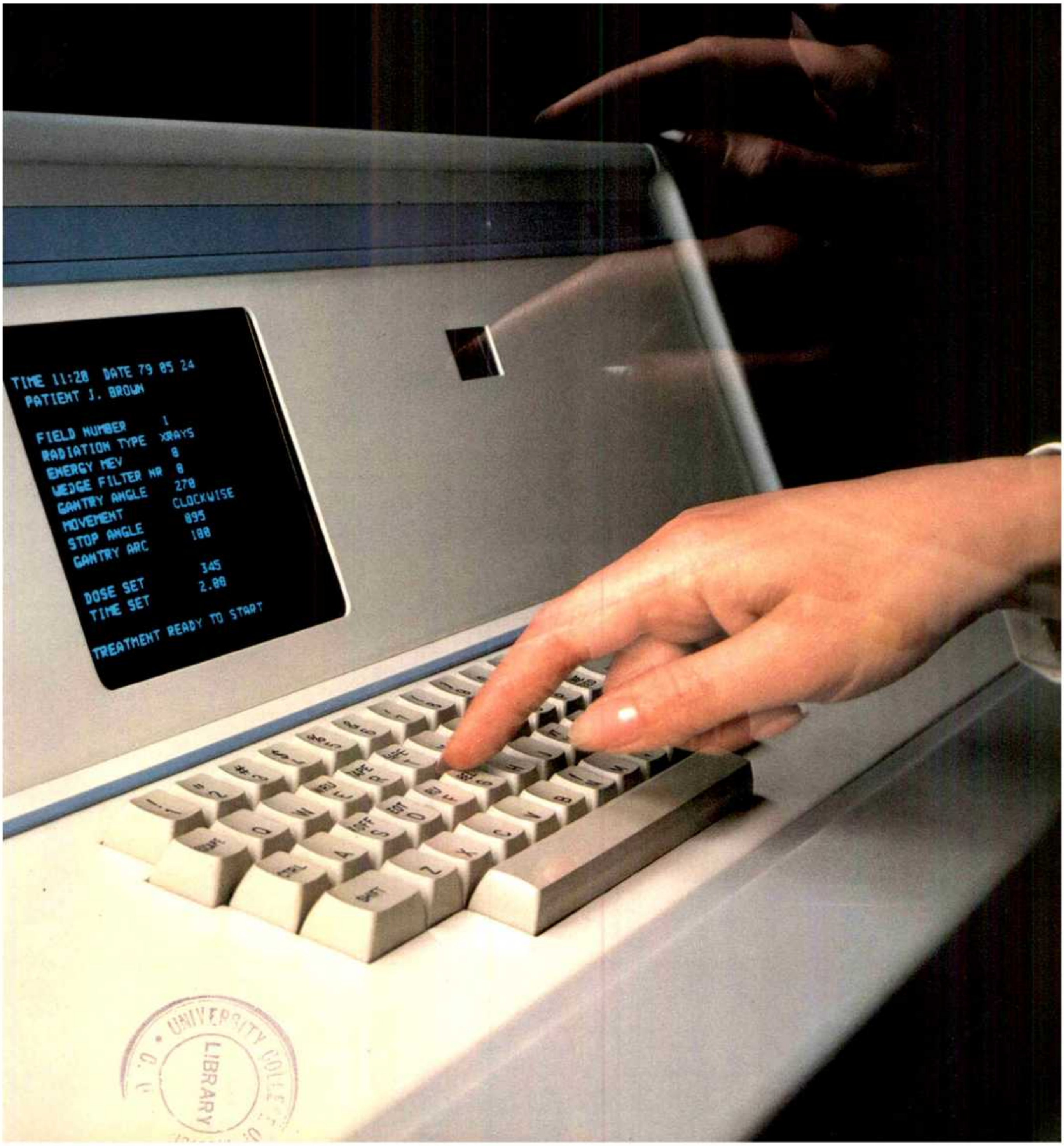

```
TIME 11:20  DATE 79 05 24
 PATIENT J. BROWN

 FIELD NUMBER      1
 RADIATION TYPE  XRAYS
 ENERGY MEV        8
 WEDGE FILTER NR   0
 GANTRY ANGLE     270
 MOVEMENT        CLOCKWISE
 STOP ANGLE        095
 GANTRY ARC        100

                   345
 DOSE SET          2.00
 TIME SET

TREATMENT READY TO START
```

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SIMPLE TREATMENT CONTROL

- * Operator confidence quickly established
- * Rapid keyboard entry of treatment data by operator command
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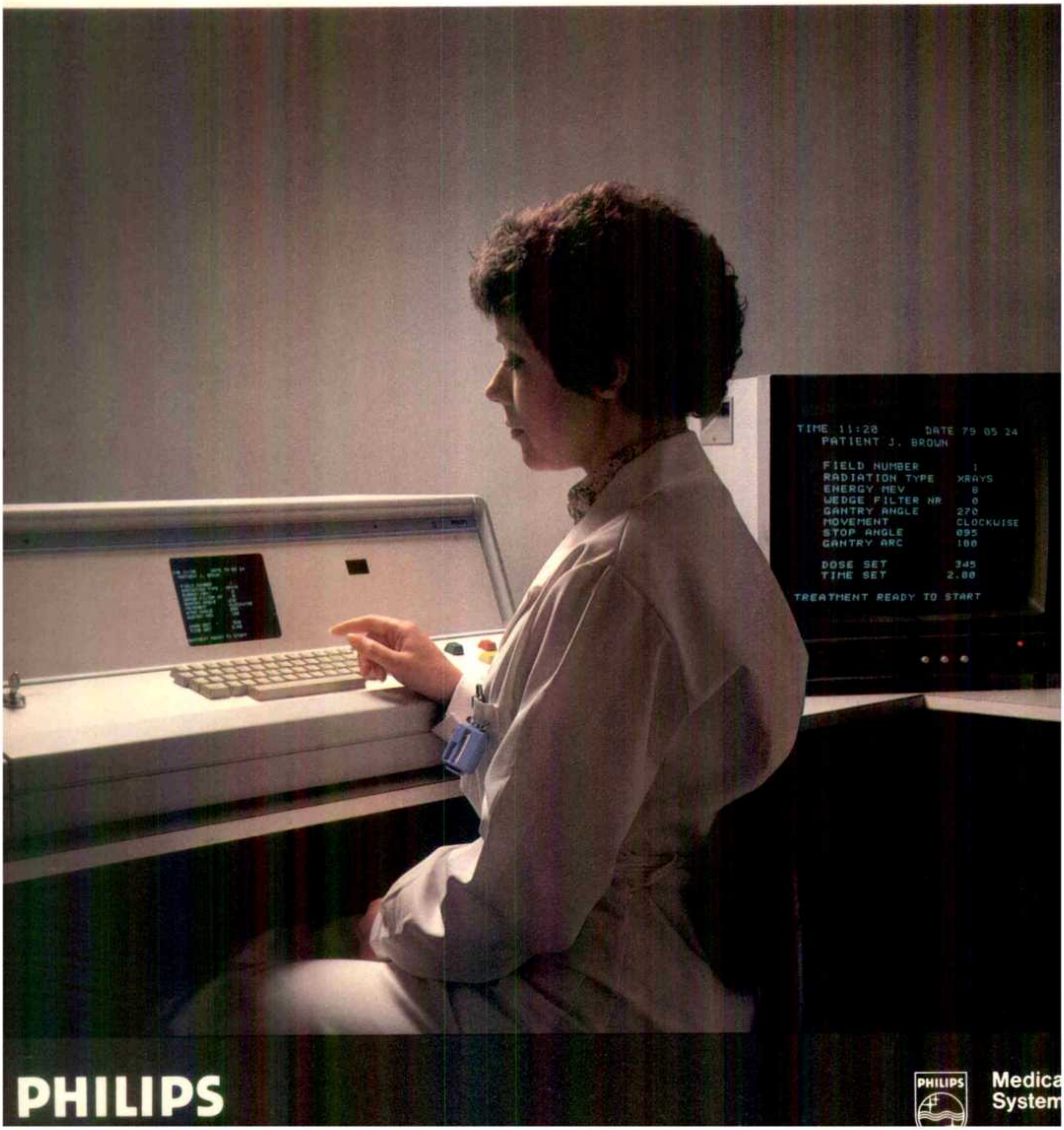
- * Fully compatible with the Philips Vericord range of automatic treatment verification and recording equipment



```
TIME 11:28        DATE 79 05 24
    PATIENT J. BROWN

    FIELD NUMBER           1
    RADIATION TYPE     XRAYS
    ENERGY MEV             8
    WEDGE FILTER NR        0
    GANTRY ANGLE         270
    MOVEMENT           CLOCKWISE
    STOP ANGLE           095
    GANTRY ARC           100

    DOSE SET             345
    TIME SET            2.00

TREATMENT READY TO START
```

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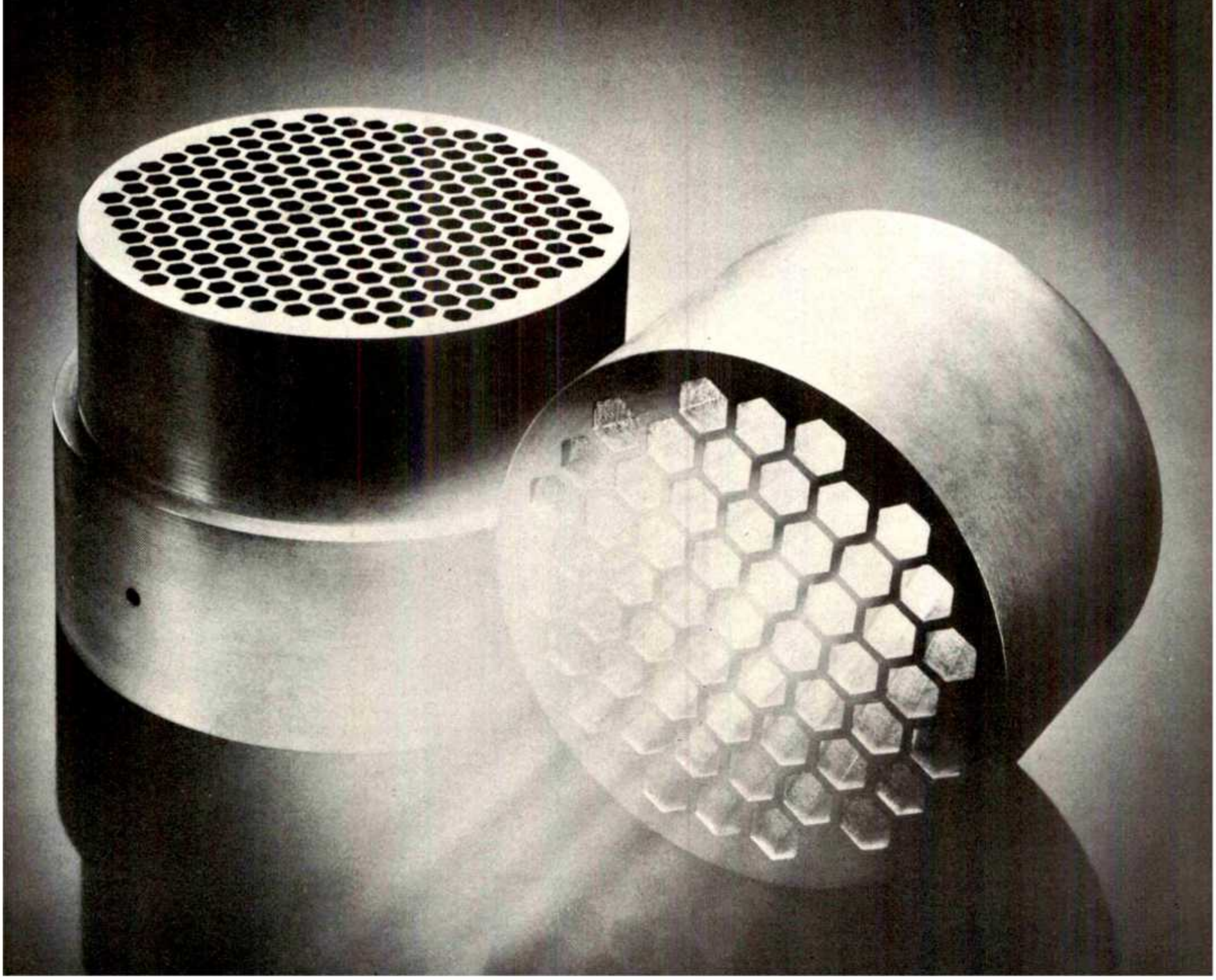

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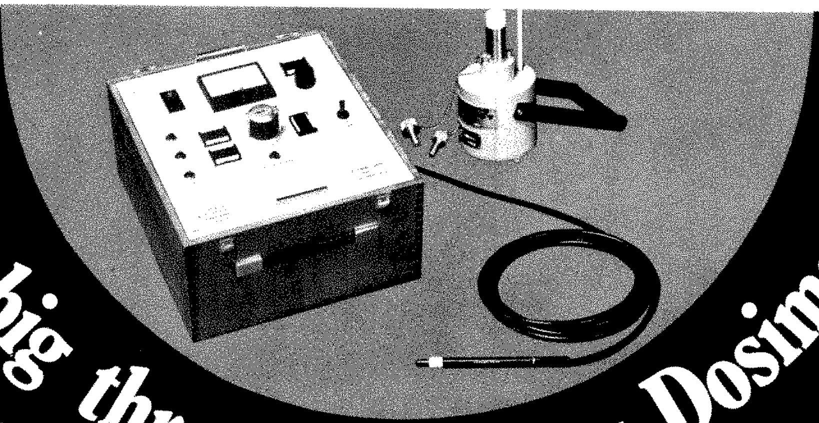

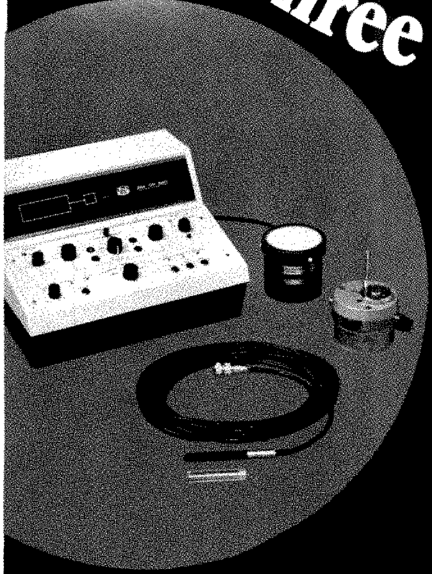

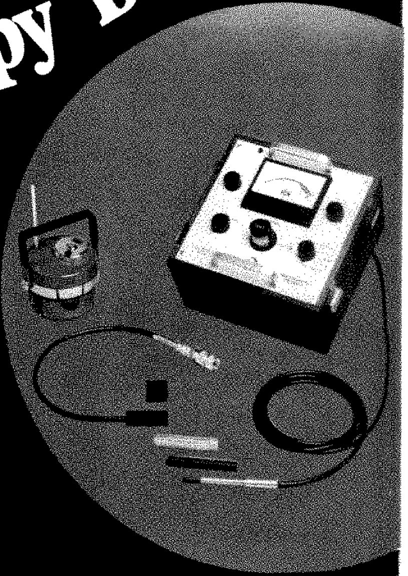

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A complete range of Instrumentation Ideal for all Radiotherapy Departments

NPL 2560 (Top)
Mains operated therapy level x-ray exposure meter. Intended for use as secondary standard when calibrated against National Primary standards. All other clinical dosemeters are referred to this secondary standard. Precision measurement of therapy levels in ranges 0-100R, 0-1000R over energy range 10kV to 35MV.

FARMER DOSEMETER 2502/3 (Right)
Battery operated clinical dosemeter ideal for all therapy machine output calibrations energy range 10kV to 35MV using standard ionisation chambers. Integrated dose measurements in range 0.1R FSD to 1k R FSD.

IONEX 2500/3 (Left)
Mains operated Dose/Doseratemeter designed to meet the needs of the therapy department both at therapy and protection levels. Provides dose, doserate, current and charge measurements. Digital display provides up to 999 reading with over range to 1999. Dose from 1mR (1000digits) to 10kR (1000 digits). Doserate 1mR/min to 10kR/min wide choice of chambers from 0.03 cc to 600 cc.

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Our caesium-137 "Manchester" afterloading system consists of X-Ray opaque PVC applicators which allow the "washer," "spacer" or "tandem" techniques to be used. The guide tubes are flexible and have a diameter of only 6.3 mm overall. Complete kits are supplied sterilized in packaging designed for maximum convenience in use.

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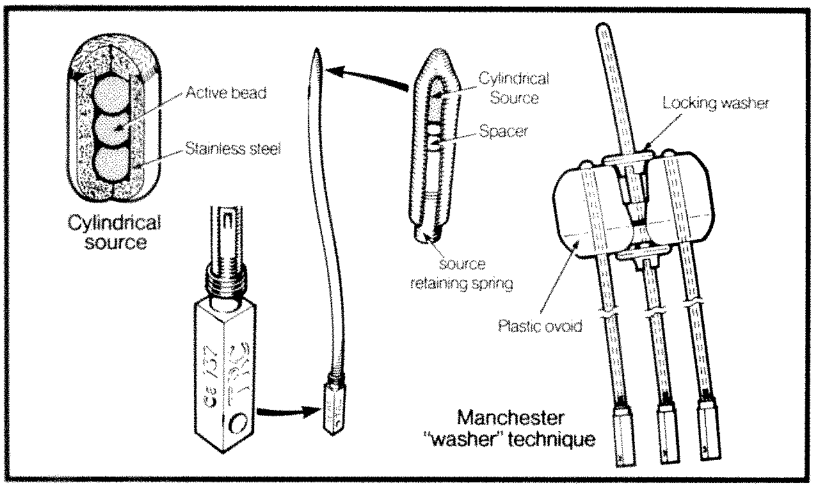

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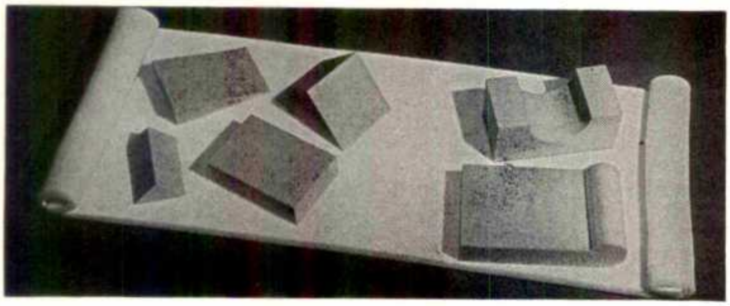

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21—24 April 1980

Four courses have been organised by the Royal Postgraduate Medical School and the Medical Research Council Cyclotron Unit, Hammersmith Hospital, on Fast Neutron Therapy. These were mainly concerned with medical aspects and the coverage of physics and dosimetry was small. Next year we are offering a course on these latter topics, together with a few sessions of more general interest.

Topics include:
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- Applications of short-lived radioactive gases.
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Most of the lectures will be given by members of the MRC Cyclotron Unit who will also be available for discussion at other times.

Course fee:
£100 including catering

Application forms may be obtained from: The School Office (SSC). Royal Postgraduate Medical School. Hammersmith Hospital, Du Cane Road, London W12 0HS Telephone 01-743 2030 ext 351.

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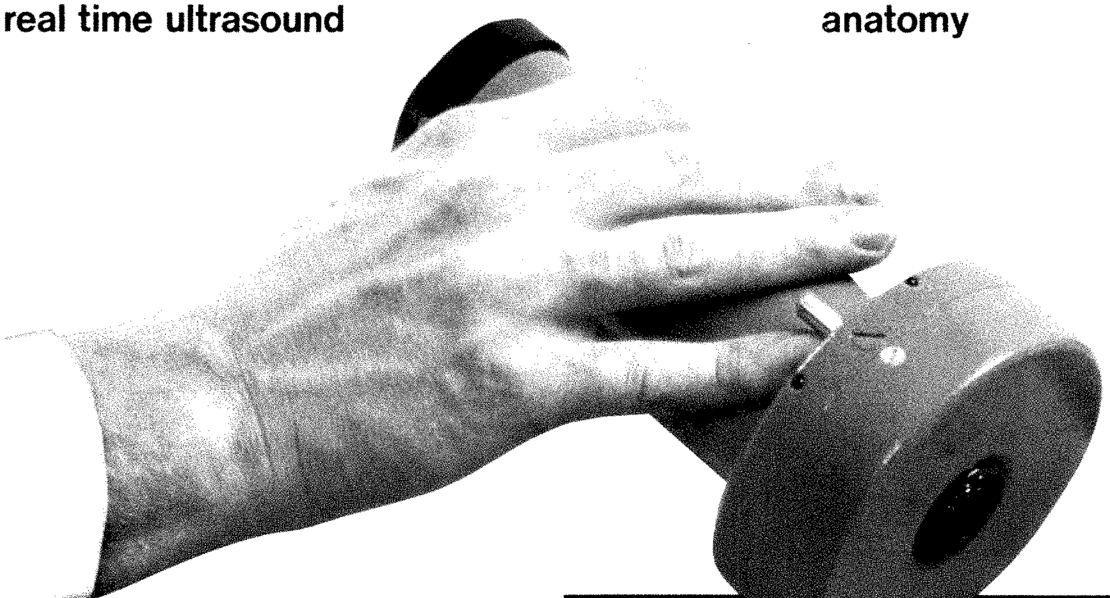

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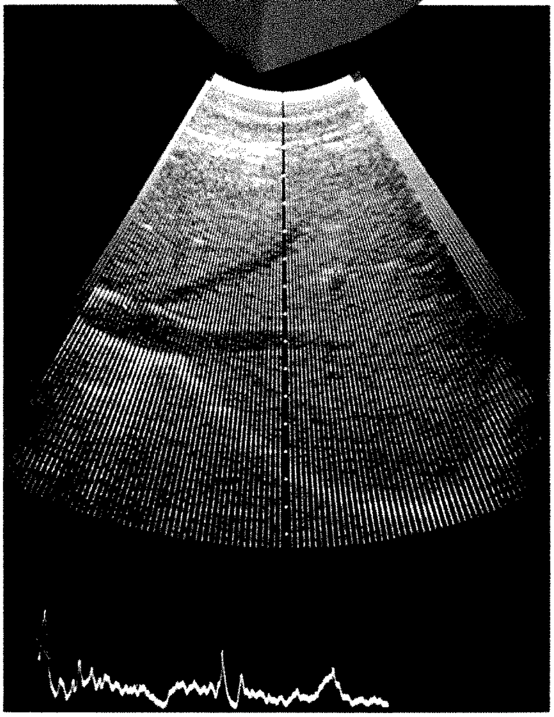

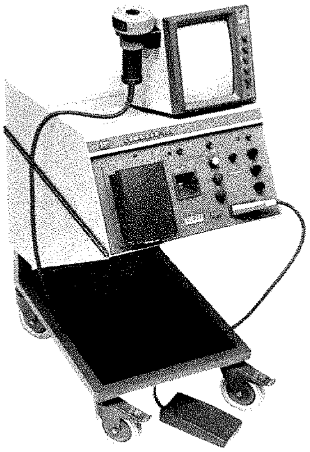

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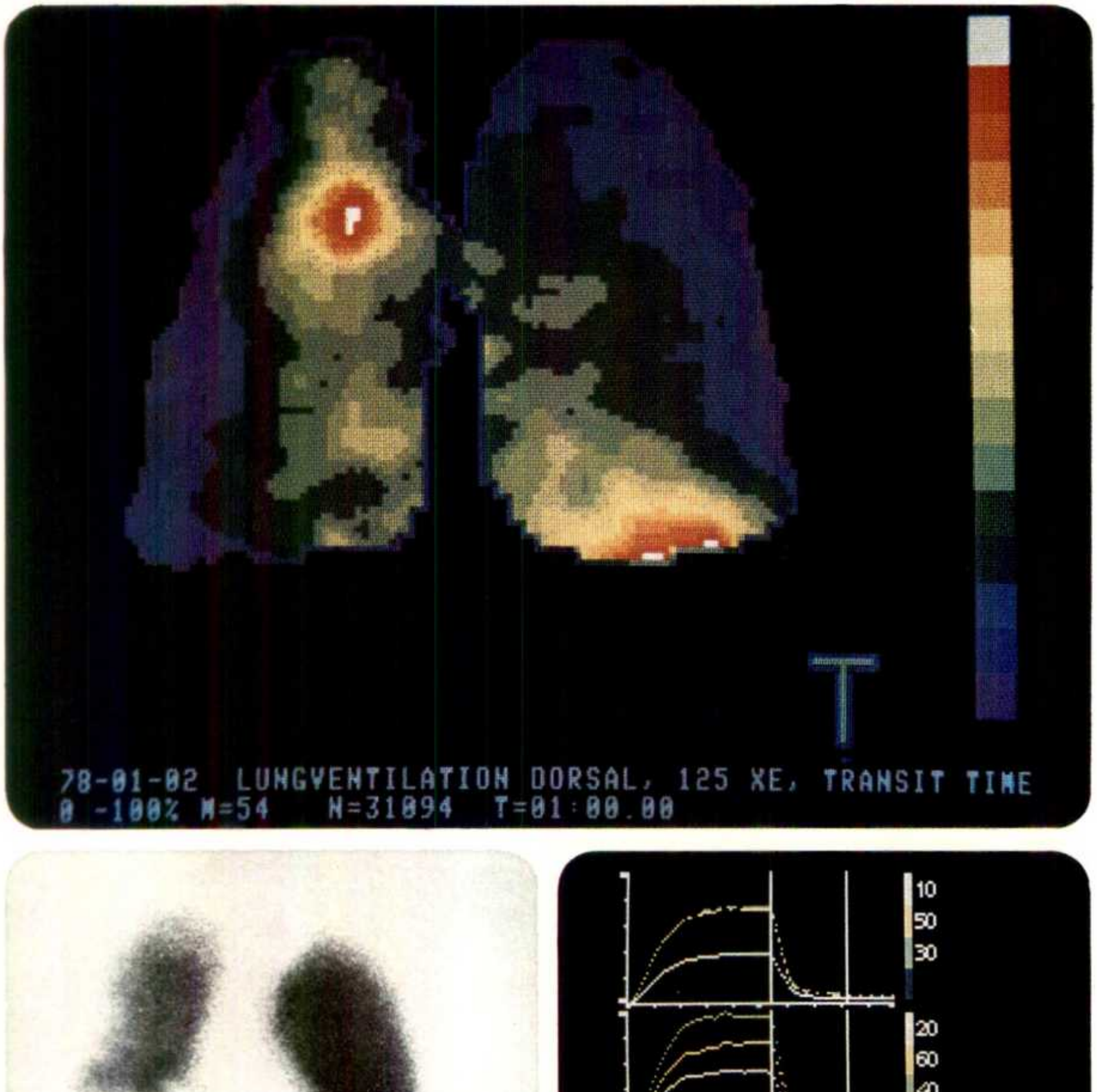

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The Philips Large Field Gamma Camera, with its full 38 cm field of view, provides high-resolution images with excellent homogeneity. The dorsal view of two lungs on a single image, shown in black and white on the left, is a typical example.

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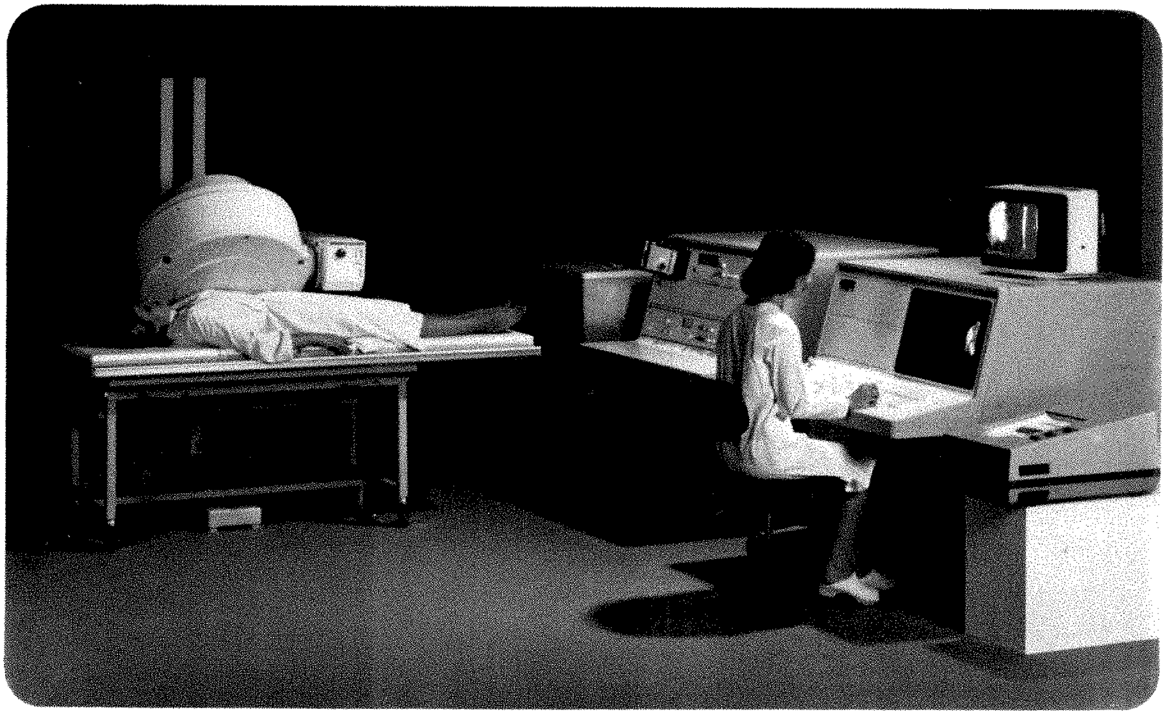
Together, the Large Field Gamma Camera and the Processing and Display System provide conclusive evidence in doubtful cases.



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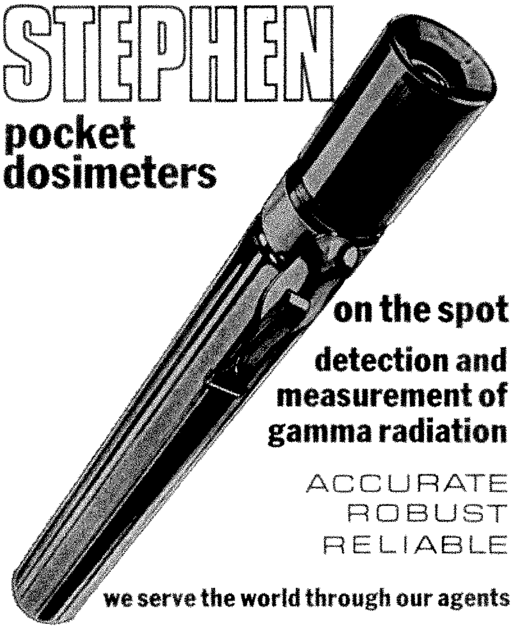

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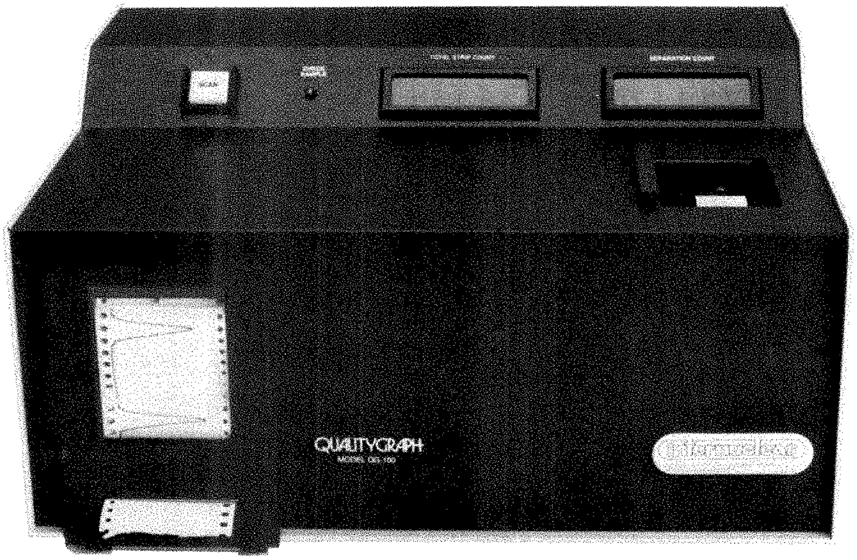

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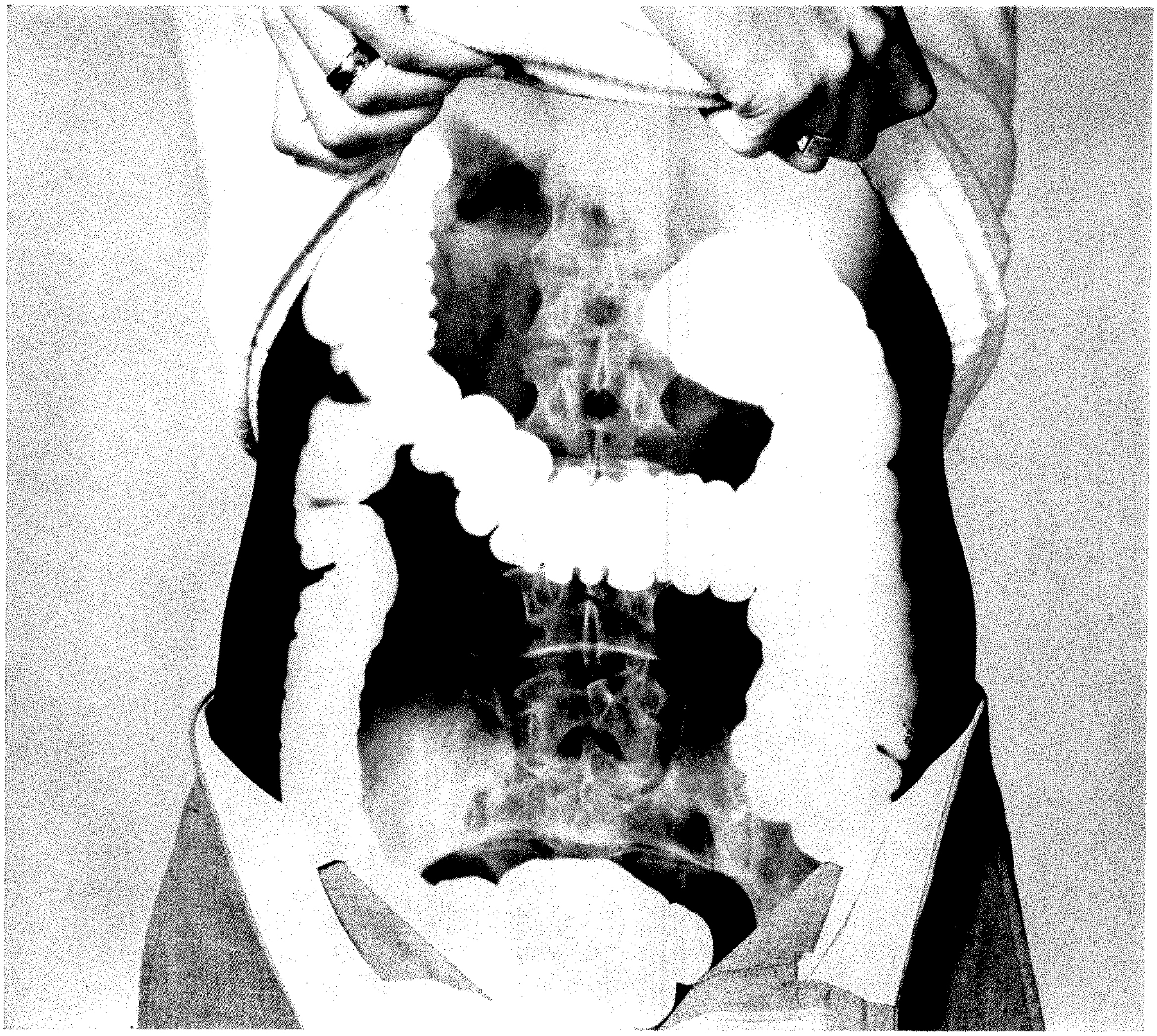

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The CT scanner in posterior fossa tumours of childhood

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(*Received April 1979*)

ABSTRACT

Eighty-five consecutive posterior fossa tumours occurring in children and detected by computed tomography (CT) were submitted to detailed analysis. There was only one false positive diagnosis, which would have been avoided with present knowledge, and no known false negative diagnoses during the same period.

In most cases the histological type of the tumour could be reliably predicted. CT was less accurate for determining the anatomical extent of the lesions but tumours arising in the brainstem could always be distinguished from those predominantly affecting the fourth ventricle and cerebellum.

ASSESSMENT

Numerous authors (Gado *et al.*, 1977; Naidich 1977; Naidich *et al.*, 1977; Wilson and Moseley, 1977; Zimmerman *et al.*, 1978) have discussed computed tomographic (CT) findings in posterior fossa tumours. Even though the posterior fossa is technically more difficult to assess than the supratentorial region, most agree that it is often possible to predict the various types of pathology. In children the great majority of posterior fossa tumours are of three histological types so that differential diagnosis using clinical and CT findings should be more simple than in adults; this tends to be supported by a large recorded series of intracranial tumours in children subjected to CT (Bilaniuk *et al.*, 1977).

At the Hospital for Sick Children, London, using EMI CT 1000 and, more recently, CT 1010 machines over 4000 paediatric CT studies have been undertaken; a detailed analysis of the posterior fossa tumours encountered in these children was performed to assess the CT criteria for the prediction of the histological type and determination of the position and extent of a tumour compared with the findings at surgical exploration or on invasive radiological procedures.

METHOD

This series included all children who had undergone a CT scan before August, 1978, in whom a diagnosis of posterior fossa tumour had been established or had been suggested on CT and excluded before March 1979. This allowed a minimum of seven months to follow the course of those brainstem lesions which were not subjected to surgery or histologically proven.

The patients were divided into two main groups; those with a tumour situated primarily in the brainstem, in which surgery was infrequently undertaken, and those in whom it was mainly situated within the fourth ventricle, vermis or cerebellar hemispheres, all of which were explored and confirmed by histology. The scan appearances were correlated with the histological diagnosis, with any pneumoencephalographic or angiographic findings and with the extent of the tumour revealed at surgery performed soon after the CT scan.

RESULTS

Infratentorial tumours constituted about 40% of all the intracranial neoplasms encountered over the period (Tables I and II). About one third of them (25) arose in the brainstem; the majority of the others were medulloblastomas (24) and astrocytomas (23), which were equally common, and ependymomas (9). There was one chordoma and one haemangioblastoma. Scans were performed in order to determine the cause of deterioration on an additional 13 patients who had previously had a posterior fossa tumour resected; a recurrence was demonstrated in only two of these and, since the major role of CT scanning in the follow-up of these cases has recently been discussed in detail (Enzmann *et al.*, 1978), they will not be considered beyond stating that the scan elucidated the problem in each case and no further diagnostic procedure was necessary.

The age range (Table III) was limited by the first hospital attendances being generally restricted to children below 14 years, and was not helpful in diagnosis. The haemangioblastoma was in a girl of 13 years, this type of tumour being rare in young children. Astrocytomas, both within the brainstem

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TABLE I

Site of tumours diagnosed by CT

Total	204
Supratentorial	121 (59.3%)
Cerebral hemisphere	54 (26.5%)
Pineal region	13 (6.3%)
Craniopharyngioma	31 (15.2%)
Optic nerve-chiasm	12 (5.9%)
Orbital	11 (5.4%)
*Infratentorial**	83 (40.7%)
Brainstem	25 (12.3%)
Others	58 (28.4%)

*Excluding two recurrent cerebellar tumours.

TABLE II

Posterior fossa tumours

Total	85
Medulloblastoma	24
Astrocytoma	23
Ependymoma	9
Haemangioblastoma	1
Chordoma	1
Brainstem mass	25
Recurrent tumour (not previously scanned)	2

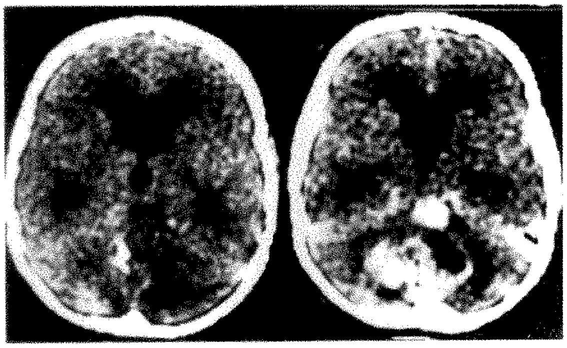

Fig. 1.

Cerebellar astrocytoma. (A) Plain scan. (B) After intravenous contrast medium. The lateral ventricles are dilated with periventricular lucency around the frontal horns. There is an irregular low attenuation mass in the right cerebellar hemisphere extending across the mid-line and apparently also involving the vermis and the left cerebellar hemisphere. There is a small peripheral nodule of calcification. There is irregular enhancement within the central parts of the low attenuation region, with ring enhancement suggesting a cyst towards the right side. At surgery the tumour corresponded to the enhancing region but was confined to the expanded right cerebellar hemisphere, displacing the vermis across the mid-line; the cystic and calcified components were confirmed.

and cerebellar hemispheres were equally common in both sexes; 90% of medulloblastomas were male and of the small group of ependymomas 80% were female. All the tumours were detected on the initial CT and there was only one false positive CT diagnosis. This was an unusually dense and enhancing inferior vermis interpreted as a tumour without mass effect, an appearance now generally recognized as a not uncommon anatomical variation (Huckman *et al.*, 1977).

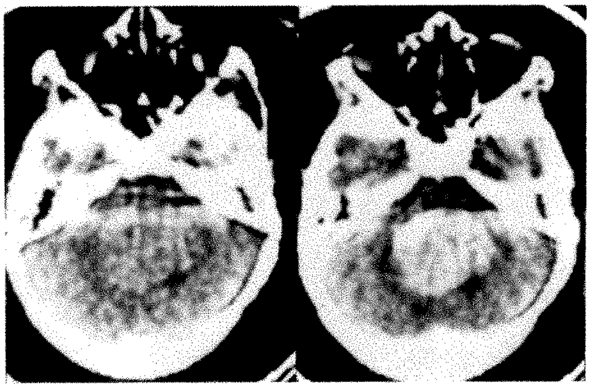

Fig. 2.

Medulloblastoma. (A) Plain scan. (B) After intravenous contrast medium. There is a large mass of slightly higher-than-brain attenuation, which enhances homogeneously with a thin surrounding rim of low attenuation; it occludes the fourth ventricle, expanding into the vermis and more into the right cerebellar hemisphere than the left, as well as compressing the brainstem anteriorly. At surgery the brainstem was invaded.

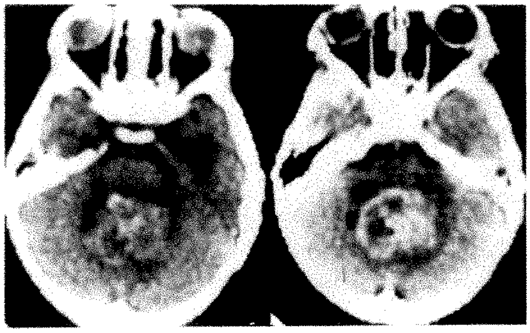

Fig. 3.

Ependymoma. (A) Plain scan. (B) After intravenous contrast medium. There is a mass of slightly higher-than-brain attenuation containing scattered calcification, which enhances irregularly, centred on the fourth ventricle. There is a rim of low attenuation around most of the mass, which is incomplete towards the left side posteriorly. The tumour filled the fourth ventricle and involved the vermis and left cerebellar hemisphere at surgery.

The tumour attenuation on the plain CT analysed in Table IV, was useful in differential diagnosis. Apart from nodules of calcification in two cases, none of the astrocytomas had high attenuation components (Fig. 1). With the exception of well-defined, usually small central non-enhancing cystic or necrotic regions, none of the medulloblastomas were of low attenuation (Fig. 2), nor were any ependymomas purely low or isodense lesions (Fig. 3). The brainstem tumours (Fig. 4) were generally of low or isodense attenuation similar to the cerebellar astrocytomas, but cystic and necrotic changes were much less frequent.

Calcification was present in four of the ependymomas and in only nine of the other tumours. The presence of calcification alone was not of as much practical help as this may suggest in assessing the likely histology since there were relatively few ependymomas (Table V). However, the type of calcification was of limited diagnostic value; it was slight in medulloblastomas; relatively diffuse calcification occurred in ependymomas (Fig. 3); isolated coarse nodules occurred in both astrocytomas (Fig. 1) and ependymomas (Fig. 7).

TABLE III

Histology	Total	Males, %	Age range (mean)
Medulloblastoma	24	88	2–13 (6.6)
Astrocytoma	23	48	1–11 (6.6)
Ependymoma	9	22	2–10 (5.3)
Haemangioblastoma	1	0	13
Chordoma	1	100	6
Brainstem masses	25	52	4/12–12 (6.6)
Total	83	60	1–13

TABLE IV

ATTENUATION RELATIVE TO BRAIN SUBSTANCE

		High	Low	Iso	Mixed
Total		21	9	14	14
Histology					
Medulloblastoma	24	15	—	3	6
Astrocytoma	23	—	9	9	5
Ependymoma	9	6	—	—	3
Haemangioblastoma	1	—	—	1	—
Chordoma	1	—	—	1	—
Brainstem	25	1 (Haemorrhage)	13	9	2

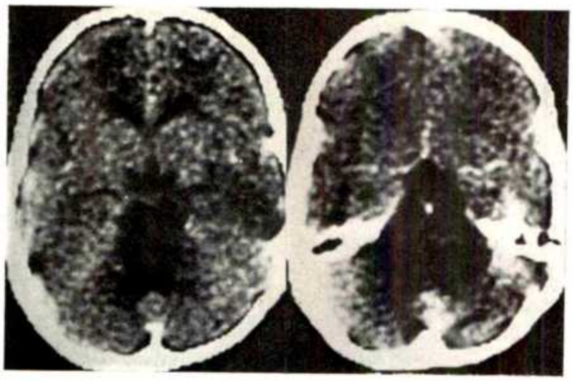

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FIG. 4.

Brainstem glioma. (A) Plain scan. (B) After intravenous contrast medium. The brainstem is expanded by a tumour of markedly diminished attenuation. There is no abnormal enhancement, but the basilar artery is shown to be embedded within the expanded substance of the pons.

TABLE V

CALCIFICATION

	Calcified, %	Distribution,%
Total	15.7	
Medulloblastoma	12	23
Astrocytoma	9	15
Ependymoma	44	31
Haemangioblastoma	—	—
Chordoma	100	8
Brainstem	12	23

TABLE VI

HYDROCEPHALUS

	No.	Per cent	Distribution,%
Medulloblastoma	23	96	38
Astrocytoma	20	90	34
Ependymoma	8	89	14
Haemangioblastoma	1	100	2
Chordoma	—	—	—
Brainstem	7	28	12

TABLE VII

PERIVENTRICULAR LUCENCIES

	No.	Per cent	Distribution,%
Medulloblastoma	9	37	31
Astrocytoma	14	61	49
Ependymoma	2	22	7
Haemangioblastoma	1	100	3
Chordoma	—	—	—
Brainstem	3	12	10

TABLE VIII

Enhancement pattern

	Diffuse	Patchy	Even ring	Uneven ring	Nodule and cyst	Nodule	None
Total	27	12	7	8	6	3	13
Histology, %							
Medulloblastoma	52	42	14	25	—	—	—
Astrocytoma	26	16	72	25	66	33	8
Ependymoma	11	—	—	25	17	33	—
Haemangioblastoma	—	—	—	—	17	—	—
Chordoma	—	—	—	—	—	—	8
Brainstem	11	42	14	25	—	33	84

TABLE IX

Cystic changes

	Cyst		Distribution
	Per cent	Cases	Per cent
Total	39	(32)	
Medulloblastoma	46	(11)	35
Astrocytoma	65	(15)*	47
Ependymoma	22	(2)	6
Haemangioblastoma	100	(1)	3
Chordoma	0		0
Brainstem	12	(3)	9

**Surgery*. In three cases the cystic appearance was due to gelatinous cellular material and not to true cysts. Five additional tumours contained cysts not shown by CT.

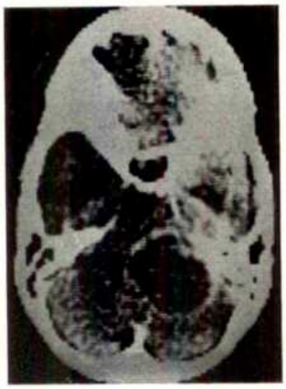

Fig. 5.

Cystic cerebellar astrocytoma after intravenous contrast medium. There is a low attenuation mass in the right cerebellar hemisphere, with ring enhancement. The fourth ventricle is not visible. The tumour was composed of a thick walled cyst containing proteinaceous fluid and corresponded exactly with the CT appearances.

Only 28% of the brainstem tumours had hydrocephalus, whereas it was present in virtually all tumours involving the fourth ventricle and cerebellar hemispheres (Table VI). Periventricular lucencies (Fig. 1) (PVL) occurred with only three of the brainstem tumours, but with 26 of the others (Table VII). In the astrocytomas it was most common in those in which cystic (10) or gelatinous (2) degeneration had occurred. Two of the three brainstem tumours with periventricular lucencies were also cystic. Such degeneration could possibly have been associated with relatively rapid swelling causing occlusion of CSF pathways and hydrocephalus to develop more acutely.

Rescanning after intravenous contrast medium was performed in all except four patients, two of these being brainstem lesions. There was considerable variation of enhancement patterns in all histological types (Table VIII). However, a ring of even thickness (Fig. 5) or a nodule adjacent to a low attenuation cyst (Fig. 6) with no enhancement of the rest of its contour, was a much more common feature of astrocytomas than other tumours. Conversely, diffuse and patchy enhancement was more common in medulloblastomas (Fig. 2). More than 50% of brainstem tumours enhanced though uncommonly to a marked degree and without any particular pattern predominating.

Well-defined regions with attenuation lower than brain, but higher than cerebrospinal fluid, which remained unchanged after intravenous contrast medium due to cystic degeneration or paratumour cyst formation (Figs. 5 and 6) were present in 65% of astrocytomas (Table IX). In three cases gelatinous degeneration and not cystic fluid was found within them at surgery. In a further five tumours, cysts discovered at surgery were not diagnosed on CT. Three of these were small and could not be visualized even in retrospect; in the other two the quality of the scans was suboptimal and in one of them contrast medium was not administered. Cystic appearances were present in three of the brainstem tumours and two

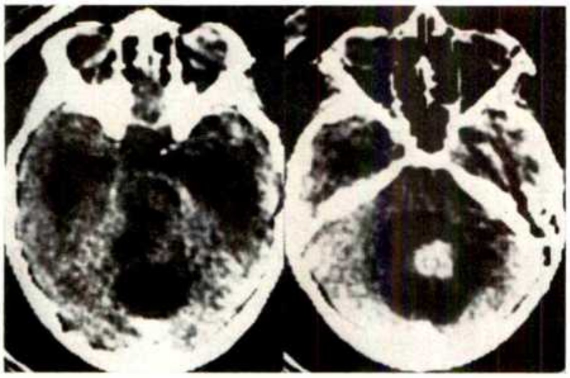

FIG. 6.

Cystic astrocytoma. (A) Plain scan. (B) After intravenous contrast medium. There is a lobulated mass of low attenuation with a peripheral enhancing isodense nodule on its right side. The tumour obliterates the fourth ventricle and involves the cerebellar vermis. At surgery the tumour was confined to the enhancing nodule and was associated with a non-tumour cyst.

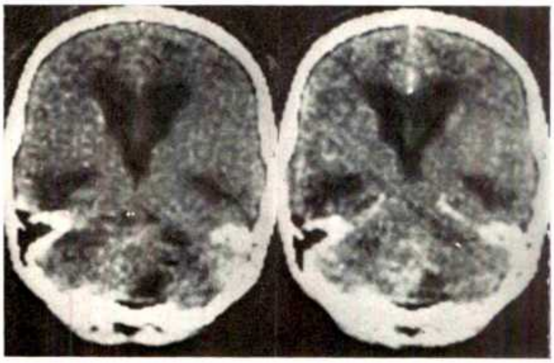

FIG. 8.

Medulloblastoma. (A) Plain scan. (B) After intravenous contrast medium. There is an ill-defined mass of slightly increased attenuation which enhances moderately after intravenous contrast medium. There is a low attenuation region towards its right posterior aspect, which does not enhance. The tumour is surrounded by a thin zone of low attenuation apart from its left border which blends directly with the cerebellar hemisphere. The fourth ventricle is occluded. At surgery the small cyst was confirmed. The tumour involved the left cerebellar hemisphere and the vermis, filled the fourth ventricle and extended into the brainstem.

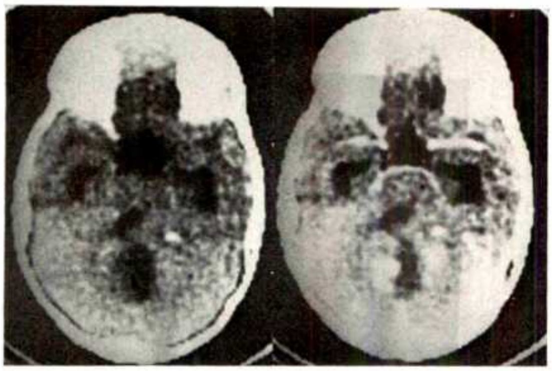

FIG. 7.

Ependymoma. (A) Plain scan. (B) After intravenous contrast medium. There is an ill-defined isodense mass, with a low attenuation centre and with a peripheral calcified nodule, within the cerebellar vermis extending into and deforming the fourth ventricle. The periphery of the mass enhances leaving an irregular unenhancing centre which was confirmed at surgery to be due to tumour necrosis. The margin of the mass blends with the cerebellum without any surrounding low attenuation and was continuous with both cerebellar hemispheres and the right middle cerebellar peduncle at surgery.

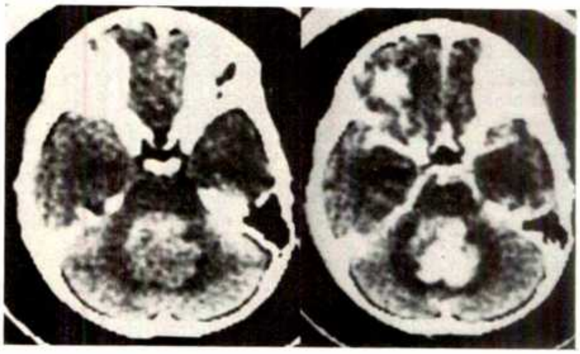

FIG. 9.

Typical medulloblastoma. (A) Plain scan. (B) After intravenous contrast medium. High attenuation homogeneously enhancing mass expanding the cerebellar vermis with low attenuation in the adjacent parts of the cerebellar hemispheres. The fourth ventricle is compressed anteriorly and almost obliterated.

ependymomas (Fig. 7); they were frequent (46%) but usually, though not invariably, of small size in medulloblastomas (Fig. 8) none of which was a predominantly cystic lesion.

In all but two medulloblastomas the enhanced region was surrounded by only a thin rim of low attenuation which appeared at surgery to correspond approximately with the tumour edge (Fig. 9); in two there was a wider low attenuation zone. Three ependymomas showed a similar thin rim of low attenuation around an enhanced region that was well circumscribed (Fig. 3) but the others were ill-defined

TABLE X

Fourth ventricular involvement

Assessment on CT		Surgical findings	
	Total	Displaced	Invaded
Displaced	24	20	4
Invaded	24	—	24
Not visible	10	5	5

TABLE XI

Hemisphere invasion

	On CT assessment	At surgery
Medulloblastoma	11	13
Astrocytoma	18	19
Ependymoma	4	5
Haemangioblastoma	1	1
Total	34	38

Four errors due to inability to distinguish invasion from expansion of vermis.

TABLE XII

Brainstem invasion

	On CT assessment	At surgery
Medulloblastoma	2	7
Astrocytoma	5	10
Ependymoma	4	7
Total	11	24

Thirteen errors. The CT findings were due to fourth filled with tumour in contact with brainstem (9).
Sectioned too high to show site of invasion (3).
Ambiguous appearances misinterpreted (1).

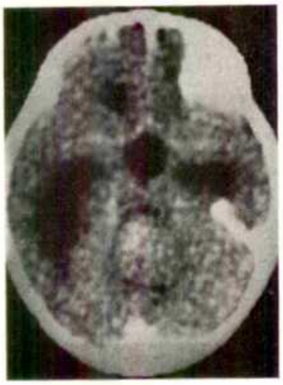

Fig. 10.

Ependymoma, after intravenous contrast medium. A well-defined tumour is outlined within the expanded fourth ventricle and was confined to it at surgery.

(Fig. 7). The amount of oedema around the enhanced components of cerebellar astrocytomas varied markedly, being absent in four, considerable in nine and minor to moderate in the others. The cerebellar astrocytoma at surgery often corresponded in extent with the enhanced region. However, in cerebellar and fourth ventricular tumours determination of the extent of the anatomical involvement by CT, based on comparison with surgical findings (Tables X, XI, XII) revealed a number of errors which could not be avoided even on review.

In all cases where tumour appeared on CT to be enclosed in a rim of cerebrospinal fluid within the cavity of the fourth ventricle this was confirmed at surgery (Fig. 10); when the fourth ventricle was not visible there was a 50% chance that it would be invaded and when it was simply displaced there was a one in six chance of finding tumour extending into it.

In tumours involving the walls of the fourth ventricle or cerebellum, it was often impossible to determine the proportion of expansive growth causing displacement of cerebellar substance and of infiltrative extension (Table XI), even when the edge of the tumour was demarcated by an unenhancing band of low attenuation (Fig. 1). Conversely, in a number of the cases without surrounding low attenuation, a tumour which appeared to merge into the cerebellar substance, was apparently not infiltrating it at surgery (Fig. 12).

Anterior penetration of tumour into the brainstem was obvious when there was posterior displacement of the fourth ventricle or extension of high attenuation or

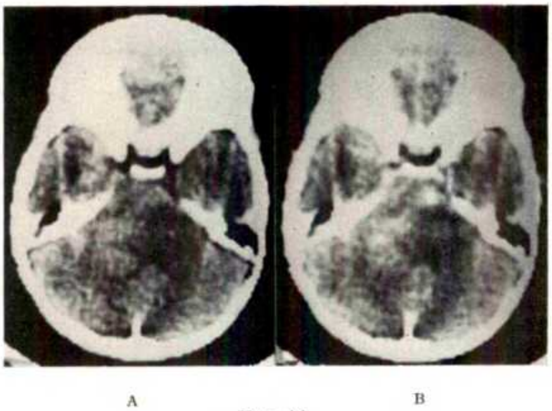

Fig. 11.

Ependymoma. (A) Plain scan. (B) After intravenous contrast medium. There is an irregular enhancing mass of slightly increased attenuation involving the anterior part of the left cerebellar hemisphere and the pons in continuity. There is surrounding low attenuation and there is also low attenuation in the right side of the pons and medial part of the right cerebellar hemisphere. The fourth ventricle is displaced to the right and slightly posteriorly.

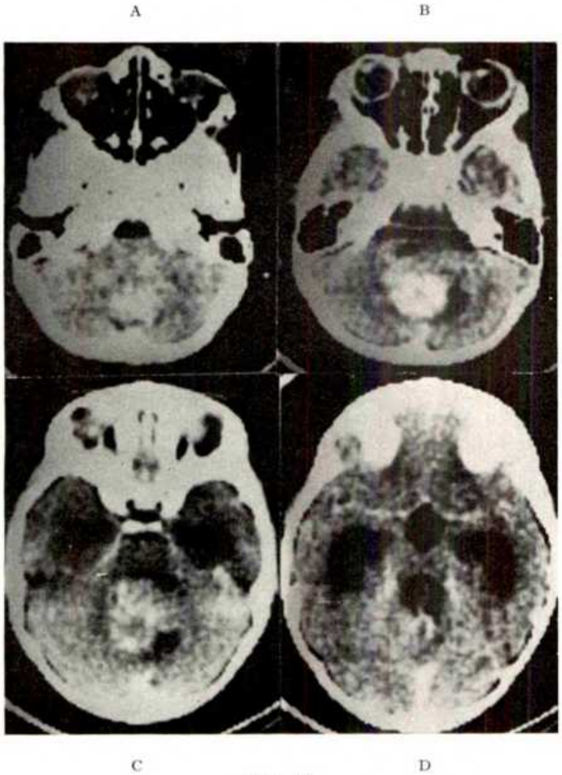

Fig. 12.

Medulloblastoma. (A, B, C, D) after intravenous contrast medium. There is a mass of increased attenuation which enhances with a low attenuation cystic component in its posterior part. Part of the mass is well-defined, but parts blend into the cerebellum and brainstem. At surgery, the mass expanded the cerebellar vermis and bulged into the dilated fourth ventricle and down into the vallecula, but the cerebellar hemispheres and brainstem were not invaded.

enhancement into the brainstem (Fig. 11), but it was difficult to assess in other cases (Table XII); particularly where a tumour in the fourth ventricle was invading the floor clear signs of brainstem involvement were frequently absent or at most ambiguous (Figs. 2 and 9). In three cases the CT sections did not extend low enough to show part of a tumour invading the medulla.

Plain skull films showed evidence of raised intracranial pressure in 30 cases (vault expansion (5), wide sutures (22), erosion of sella (7)). Calcification was visible in three tumours, all ependymomas, in all of which it was shown on CT.

Vertebral angiography in 11 patients, including six with brainstem tumours always confirmed a mass, but, despite subtraction, showed no evidence of pathological circulation in any case. Distortion of vessels outside the extent of the abnormality revealed by the CT scan was shown in three of the brainstem tumours, but in no patient with a cerebellar hemisphere tumour did angiography contribute significant information, beyond that obtained from the CT.

Air studies were performed in 12 patients, including nine brainstem tumours and were diagnostic in all cases. They gave more concise localization than CT in seven of the brainstem tumours by showing previously undetected involvement of the upper brainstem (6), and/or medulla (3) or more extensive anterior extension (3) of the tumour.

Discussion

In many cases it is possible to suggest the histological type of tumour from the plain and enhanced scans in the clinical context. Medulloblastoma occurs in young boys; the male incidence was even greater than usual in our series, but the tumour is generally considered to be twice as common in males. In children it usually forms a slightly higher-than-brain attenuation well circumscribed mass, most frequently in the inferior vermis and involving the fourth ventricle, with a narrow halo of oedema. It enhances homogeneously or patchily and cystic or necrotic components are usually small.

Cerebellar astrocytoma occurs equally in the sexes affecting a wider age range, but commonly children or young adults. It is a low attenuation, typically hemispheric mass, often with a considerable cystic component. The type of enhancement varies, but an even ring with variable surrounding oedema or an enhancing nodule adjacent to a cyst with a non-enhancing rim occurring in a child should suggest the diagnosis.

Ependymoma may occur at any age and is slightly commoner in females. It is usually adjacent to and involves the fourth ventricle often extending through the lateral recesses or vallecula and is most frequently of increased attenuation with calcified components.

CT has limitations in precise delineation of the anatomical extent of posterior fossa tumours, but it allows separation of the cerebellar and fourth ventricular tumours from pure brainstem gliomas, in which the management differs. In most cases children with cerebellar and fourth ventricular tumours will be subjected to exploration and removal of much of the mass in order to reduce local pressure and relieve hydrocephalus. Moderate under-estimation of the extent of the tumour is unlikely to alter the management. Failure to diagnose inferior extensions of tumours was apparently due in some cases to not including the foramen magnum region in the sections. The importance of attempting to section the whole extent of the tumour is obvious and is technically easier with general purpose scanners.

It may appear to be unreasonable to rely on CT alone for confirmation of the clinical diagnosis of a brainstem tumour, but in practice biopsy is hazardous unless there is a large cystic or necrotic, or a major extra-axial component. Other radiological procedures, although confirming the presence of a mass and clarifying its extent, are rarely specific for neoplasm and give less information about the nature of the mass than the attenuation coefficients. Brainstem encephalitis and demyelination may present with low attenuation regions generally without any mass effect or enhancement after contrast medium. The clinical signs and cerebrospinal fluid analysis may elucidate. Response to radiotherapy and steroids, follow-up scans or autopsy eventually support or exclude a diagnosis of tumour.

Plain skull films made no significant diagnostic contribution in these cases and it is apparent that vertebral angiography now plays a very limited part in the diagnosis of posterior fossa tumours in children below 14 years of age. It should be performed if there is a reasonable possibility of an angiomatous malformation. This may be suggested either by a history of one or more acute episodes of deterioration or by attenuation changes consistent with haematoma or enlarged vessels (Kendall and Claveria, 1978). It is also of diagnostic value in children with suspected haemangioblastoma, though these tumours almost invariably present at a later age, and it may be of technical significance in planning a surgical approach to extrinsic components of brainstem gliomas or the rare extra-axial masses.

Additional information about the extent of a tumour may be obtained from pneumoencephalography and may be considered important in planning radiation therapy, although this is usually possible from a combination of CT and clinical findings. There were, by chance, no tumours in this series in which CT was negative. There were, however, several cases in which pneumoencephalography was performed despite negative CT to exclude clinically suspected small tumours with greater certainty. Pneumoencephalography with multi-directional tomography gives higher resolution than CT and it may be indicated in selected cases when CT is equivocal or negative. The only false positive assessment in this series, which has already been referred to, was in an early case; it is rarely necessary to confirm the presence of a positive CT mass lesion by any other study.

Acknowledgments

We are very grateful to our surgical colleagues Mr. Kenneth Till and Mr. Norman Grant for free access to their operative findings. We thank also Mrs. Suzanne Pink for secretarial assistance.

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1979, *British Journal of Radiology*, *52*, 777–780

Myelographic features of the normal sacral sac

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ABSTRACT

One hundred and sixty normal sacral sacs at myelography have been studied and the results analysed statistically. The features which may have clinical relevance are discussed.

A case of primary sacral tumour first presenting with slight deviation of the sacral sac from the mid-line on myelography, prompted a search for the normal range of measurements in this region. Standard reference works on radiological measurements (Lusted and Keats, 1972) and myelography (Shapiro, 1968) did not provide details. Anatomical studies of the lumbosacral canal, based on cadavers, have produced some measurements (Dommisse, 1975), but myelographic series have concentrated chiefly on the cervical canal (Porter, 1956).

The present study was undertaken to establish measurements in normal adults, as seen on myelography.

METHOD

Of 682 myelograms performed at the Royal United Hospital, Bath over a period of approximately ten years, the radiographs of 335 patients were available for review. The criteria used for final selection were:

1. Only erect AP and lateral views of the sacral sac, *i.e.* distended with contrast medium, were used.
2. Radiographic end-points, both bony and soft tissue, were clearly defined.
3. Contrast medium was within the sub-arachnoid space, *i.e.* not extra- or sub-dural.
4. No bony anomalies, *e.g.* spondylolisthesis, were present.
5. No abnormality was shown in the sacral region, *i.e.* below the LV5/S1 disc space.

A total of 160 cases were considered to have fulfilled the above criteria. These were analysed for the following points:

1. *On the AP view* (Fig. 1) an inter-pedicular line was drawn between the mid points of the medial borders of the pedicles of the first sacral segment. A line at right angles to this was taken as a perpendicular. Measurements were then made of

(i) deviation of the tip of the sacral sac from the perpendicular (a);

(ii) width of the sac at the midpoint between the inter-pedicular line and the tip of the sac (b).

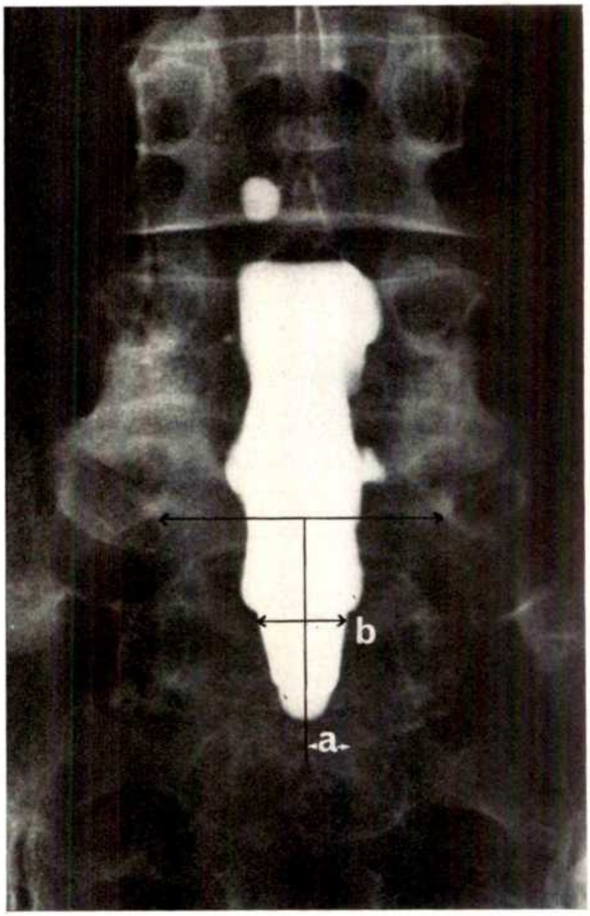

FIG. 1.

AP view. (A) Deviation, if present, of the tip of the sacral sac from the perpendicular.
(B) Width of the sac.

2. *On the lateral view* (Fig. 2) the upper margin of the body of the first sacral segment was projected backwards to the posterior margin of the vertebral canal. A line was drawn at right angles to this to the tip of the sacral sac. Measurements were then made of

(i) the distance along this line from the upper border of the sacrum to the tip of the sacral sac (y);

(ii) the sagittal diameter at the mid point of the line between the upper border of the sacrum and the tip of the sac (x).

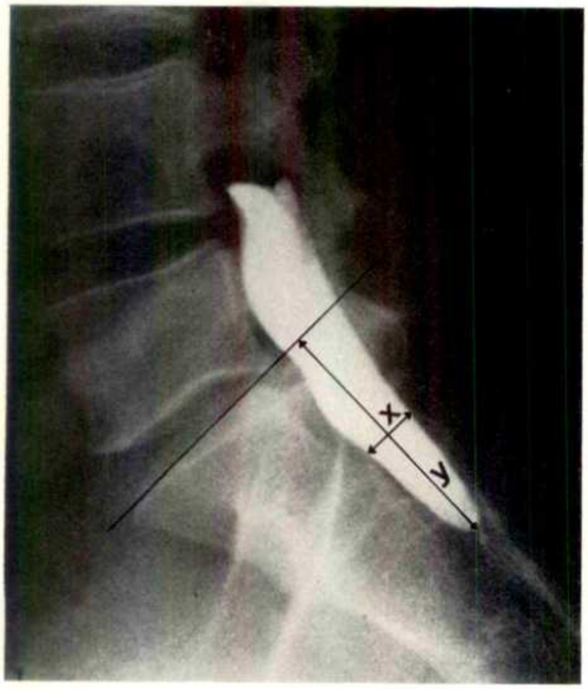

FIG. 2.
Lateral view. (X) Sagittal diameter. (Y) Length of sac.

TABLE I

TABLE OF PROBABILITIES THAT ALL MEASUREMENTS OF A PARTICULAR TYPE ARE FROM A COMMON POPULATION

	Probability	
	By age	By sex
1(a) AP width	0.40	0.22
(b) Variation from 1r	0.69	0.13
(c) Root sheaths	0.60	0.85
(d) Termination of sac	0.77	0.25
2(a) Sagittal width	—	0.80
(b) S1/tip length	0.04	0.82
(c) Relation to sacrum	0.17	0.60
(d) Level of termination	0.55	0.65

TABLE II

TABLE OF POPULATIONS FOR MEASUREMENTS OF S1/TIP LENGTH FOR BOTH SEXES, WITH AGE

Age	<4.0 cm	>4.0 cm	Total
0–30 years	11	16	27
31–50 years	24	51	75
51+ years	9	49	58
Total	44	116	160

The sacral level of termination of the sac was also recorded.

3. Filling of nerve root sheaths.

4. Parallelism between the anterior wall of the sac and the bony sacrum. Actual measurements between the anterior wall and the posterior margin of the sacrum were not undertaken, as it was considered that, while theoretically of value, the measurements would be small and thus substantially increase the magnification error.

5. Presence of sacral perineural cysts.

6. Termination of the sac, *i.e.* blunt or sharp.

The radiographs assessed had been exposed during fluoroscopy following sub-arachnoid injection of 6–9 ml of iophendylate (Myodil). Similar results might be expected using meglumine iocarmate (Dimer-X) or metrizamide (Amipaque), though these water-soluble compounds might not distend the sac to the full extent obtained with an oily contrast medium. The majority of the examinations were performed on a Philips Diagnost 70. The focal spot size of the tube was estimated to be 0.6 × 0.7 mm, using a 3-slot test grid. The anode-to-spine and spine-to-film distance will vary to some extent in each case, but as the technique of obtaining erect AP and lateral views is reasonably standardized, it is not considered that a significant variation in measurements resulted. With a focus-to-couch distance of 45 cm, the range of linear magnifications for lateral views is 1.25 to 1.30, and for AP views is 1.30 to 1.36.

RESULTS

Statistical analysis of the results was carried out on each measurement set in the following way. The results were organized by sex, pooling all ages, and by age, pooling both sexes, in such a way that the expected population in any compartment exceeded five. A chi-squared test was carried out on each set of populations to determine the probability that the sets of populations were, in fact, statistically part of the same set. Thus a high probability value indicates that it is probable that the populations of the sets come from the same total population, that is that there is no variation by age (or by sex). Conversely, a low probability indicates that it is probable that the populations of the sets do not come from the same total population, or in other words, that there is a variation with age (or with sex). A summary of the values of probability p is given in Table I.

The most significant probability figure is that for the variation of S1 to tip length, with age. A chi-squared test for population match was carried out on the data shown in Table II, in which the populations in three age bands and two dimension bands are presented. With increasing age, the S1–tip length

TABLE III

SUMMARY OF ALL MEASUREMENTS

1. *AP view*

(a) Width at the mid-point

	< 1 cm	1–2 cm	> 2 cm
n	1	99	60
%	0.6	61.9	37.5

(b) Variation from perpendicular

	0	< 0.5 cm	0.5–1.0 cm
n	95	55	10
%	59.4	34.4	6.3

(c) Root sheaths

	Filled	Not filled
n	27	133
%	16.9	83.1

(d) Dural cysts

	Present	Absent
n	3	157
%	1.9	98.1

(e) Termination of sac

	Blunt	Sharp
n	97	63
%	60.6	39.4

2. *Lateral view*

(a) Sagittal diameter

	< 1 cm	1–2 cm	> 2 cm
n	6	137	17
%	3.8	85.6	10.6

(b) Length from upper border of S1 to tip of sac

	< 2 cm	2–4 cm	4–6 cm	6–8 cm	> 8 cm
n	8	36	68	40	8
%	5.0	22.5	42.5	25.0	5.0

(c) Relation to back of sacrum

	Parallel	Not parallel
n	51	109
%	31.9	68.1

(d) Sacral level of termination

	S1	S2	S3	S4
n	28	111	20	1
%	17.5	69.4	12.5	0.6

increases and this change is statistically significant with a probability $p=0.04$ of the data being from a common set. There are other trends indicated in Table I. There are indications of sex differences in AP width, variation from perpendicular, and position of termination of the sac. However, the probabilities in these cases do not justify a strong statement about these trends. Similarly there is some evidence that, with increasing age, the sac becomes more parallel with the back of the sacrum. The gap in the table of probabilities indicates that it was not possible to carry out a viable chi-squared test on this set of data.

The complete pooled results for 160 measurements are summarized in Table III. This table gives totals for all ages and both sexes and the percentage in each band chosen.

DISCUSSION

Several points emerge which may have some clinical relevance.

In both sexes, the sac was either mid-line or within 5 mm of mid-line. In no case was the deviation greater than 1.0 cm. A deviation from the mid-line of the tip of the sac of more than 1.0 cm should thus be regarded as abnormal.

The anterior margin of the sacral sac was not parallel to the sacrum in 68.1% of our cases. Thus a mid-line prolapsed lumbo-sacral disc may be missed here, and conversely a normal divergence of the sac may be mistaken for a prolapsed disc.

The root sheaths filled in only 16.9% and this lends support to the view that water-soluble compounds are more appropriate to demonstrate these. Symmetry of filling was not assessed.

The increase in length of the sac with increasing age is somewhat surprising, as the reverse might have been expected, due to osteoporosis of the surrounding bones. A loss of tension or elasticity in supporting ligaments may be the reason.

Sacral perineural cysts occur infrequently (1.9%).

The statement that "the sub-arachnoid space ends at the lower border of the second sacral vertebra" (*Gray's Anatomy*, 1973) is verified, though 30.6% of our cases terminated above or below this level.

ACKNOWLEGMENTS

We are grateful to Miss Barbara Horne for the typescript; Miss Angela Harwood and Miss Nicola Kyte for clerical assistance, and Mrs. Gina Machin for the illustrations.

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Book reviews

Medical Data Transmission by Public Telephone Systems. Editors H-J v. Mengden and H. Just, 2nd International Symposium, Mainz 1977, pp. x + 137 (Urban & Schwarzenberg, Munich) £12·50/DM48.
ISBN 3-541-70961-8 (Munich) 0-8067-0961-8 (USA)

The public telephone system, originally designed for voice communication, is being increasingly used for the transmission of medical data. This report, on the current status of medical data transmission over telephone lines, consists of 23 contributions almost all of which are devoted to the transmission of electrocardiograms either for computer interpretation or pacemaker surveillance. In the first category three-channel analogue electrocardiogram transmission systems are widely used for transmitting diagnostic electrocardiograms to a central computer for interpretation with the reports also being sent back by telephone line. The technical requirements for such systems are discussed together with the experience obtained with these systems in the UK, the USA and Europe. Indecision over uniform standards for medical analogue data transmission has been overcome by the introduction of the CCITT V16 recommendation which is covered in detail at the end of the report. This recommendation states the technical requirements for both three- and single-channel analogue transmission systems and interfaces. The question of analogue versus digital transmission is taken up by a number of contributors. While it is generally agreed that digital techniques offer the best results a few consider that it will be some time before they reach the same level of acceptability as present analogue techniques.

A number of practical working systems for the remote monitoring of pacemaker performance are also described. Most of these are single channel units which monitor the patient's electrocardiogram at home and transmit it to a cardiac test centre where a clinician can assess the pacemaker performance.

This report is likely to be of most interest to medical physicists and engineers directly involved in the problems associated with electrocardiogram transmission over telephone lines. However, it may also find a wider readership amongst medical staff interested in practical systems for remote pacemaker surveillance.

M. P. WATTS.

Nuclear Medicine Science Syllabus. Prepared by Nuclear Medicine Science Syllabus Subcommittee of the Education and Training Committee, Society of Nuclear Medicine, pp.169, 1978 (The Society of Nuclear Medicine, New York), $30.30.
ISBN 09-32004-01-6

The planning of appropriate training for work in nuclear medicine is currently topical. Discussions at various levels of formality are taking place, or have recently taken place, on how best to equip doctors for work in this field. Thought is also being given to how best to train physicists and pharmacists who are essential collaborators in a nuclear medicine service as well as how to train technical staff who are also required. It is also still an open question whether there should be a third kind of radiographer for this work or whether nuclear medicine training should be an addition following the acquisition of the Diploma of The College of Radiographers.

This volume will be useful to all those planning training courses in nuclear medicine as well as to those teaching on such courses. It has been produced by the Nuclear Medicine Science Syllabus Subcommittee of the (US) Society of Nuclear Medicine and hence is highly authoritative. The considerable thought which went into its compilation is obvious to even the most casual reader and a person using the book for reference should be prepared to make a commensurate effort when integrating the material provided with the special requirements of a specific course he is helping to evolve.

The book is written for a USA readership so is naturally influenced by practice in that country. For this reason alone a course in another country would be unlikely to be appropriate if "blindly" adopted from this book. An obvious example is Section V where teaching concerning regulations and licensing would need to be related to the laws of the country where the student intends to practise. Similarly bibliographies provided to students would also need variations from suggested lists, admirable and useful though these are. The book is, however, strongly recommended to all engaged in training personnel for work in nuclear medicine, whether the course concerned is aimed at medical, scientific, or radiography staff.

E. S. WILLIAMS.

1979, *British Journal of Radiology*, 52, 781–786 OCTOBER 1979

A clinical trial of a new low osmolality contrast medium

Sodium and meglumine ioxaglate (Hexabrix) compared with meglumine iothalamate (Conray) for carotid arteriography

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ABSTRACT

The discomfort of cerebral arteriography is due mainly to the osmolality of the contrast medium injection. A new low osmolality contrast medium—Hexabrix (32% iodine)—sodium and meglumine salts of ioxaglic acid was compared with Conray 280 (28% iodine)—meglumine iothalamate for carotid arteriography in 33 conscious patients. 30 patients preferred the ioxaglate solution which caused significantly less sensation of heat. Three patients could not distinguish between the two media. No patient preferred iothalamate.

Ioxaglic acid is a newly synthesized mono-acid dimer. Its salts produce the same osmolality as non-ionics (*e.g.* metrizamide), and one third of the osmolality of currently used mono-valent salts (*e.g.* meglumine iothalamate) in solutions of the same iodine content. Low osmolality contrast media have significant clinical advantages and will probably become the media of choice for arteriography and venography.

This investigation reports the result of a clinical trial of the acceptability to the conscious patient of a new low osmolality contrast medium for direct puncture carotid arteriography. This is believed to be the first clinical report concerning this new contrast medium —Hexabrix—(sodium and meglumine ioxaglate)— to emanate from the United Kingdom.

Cerebral arteriography by direct puncture in the conscious patient is an uncomfortable and sometimes even painful procedure. The discomfort arises partly from the technique of inserting a needle (or cannula) into the carotid (or vertebral) artery, and partly from the sensation produced by the contrast medium coursing through the arterial tree. In the last few years, there has been an increasing tendency to use general anaesthesia for direct cerebral arterial puncture, or alternatively to use trans-femoral arterial catheterization of the cerebral arteries. If the trans-femoral catheterization is performed under local anaesthesia, there is still the discomfort caused by the contrast medium flowing through the cerebral arterial tree.

There is therefore an acknowledged requirement for a contrast medium which causes little discomfort when injected into the cerebral arteries of the conscious patient. Much of the discomfort is due to vasodilatation of the vessels of the soft tissues of the scalp, face and neck. Arteriography of the external carotid artery is therefore considerably more uncomfortable than arteriography of the common or internal carotid artery.

Vasodilatation following contrast medium injection into an artery is very considerably influenced by the osmolality of the contrast medium—the greater the osmolality, the greater the peripheral vasodilatation (Hilal 1966; Grainger and Wexler (1968) unpublished data; Lindgren *et al.*, 1968; Coel and Lasser 1971; Grainger, 1971).

In the last decade, the great importance of the osmolality of contrast medium has become increasingly appreciated. Current monovalent contrast medium salt solutions have an osmolality of 5–8 times that of plasma. Several new iodinated organic compounds, each providing solutions of markedly lower osmolality than current conventional contrast media have recently been synthesized and are now becoming available for evaluation of intravascular use. As anticipated, these new low osmolality contrast media produce far less vasodilation than conventional media (Almen and Tragardh, 1971).

A clinical trial was therefore instituted comparing one of these new low osmolality iodinated compounds—sodium and meglumine ioxaglate (Hexabrix 320) with meglumine iothalamate (Conray 280) for direct puncture carotid arteriography in the conscious patient.

PATIENTS AND METHOD

Thirty-three patients were examined by percutaneous carotid arteriography by the author between August 1978 and February 1979. The details of the

TABLE I

AGE AND SEX OF PATIENTS UNDERGOING CAROTID ARTERIOGRAPHY

Age (years)	20–40	41–60	60+
Male	4	14	4
Female	2	6	3

patients are shown in Table I. A total of 156 injections of contrast medium were made: 78 of meglumine iothalamate (Conray 280) and 78 of sodium and meglumine ioxaglate (Hexabrix 320).

The patients were all conscious and received premedication of papaveratum 20 mg and scopolamine 0.4 mg. They were all sufficiently alert at arteriography to collaborate and to assess the discomfort of each arterial injection. Patients whose consciousness or intellect was sufficiently impaired, or who were rendered too drowsy by the premedication to collaborate effectively, were excluded from the study.

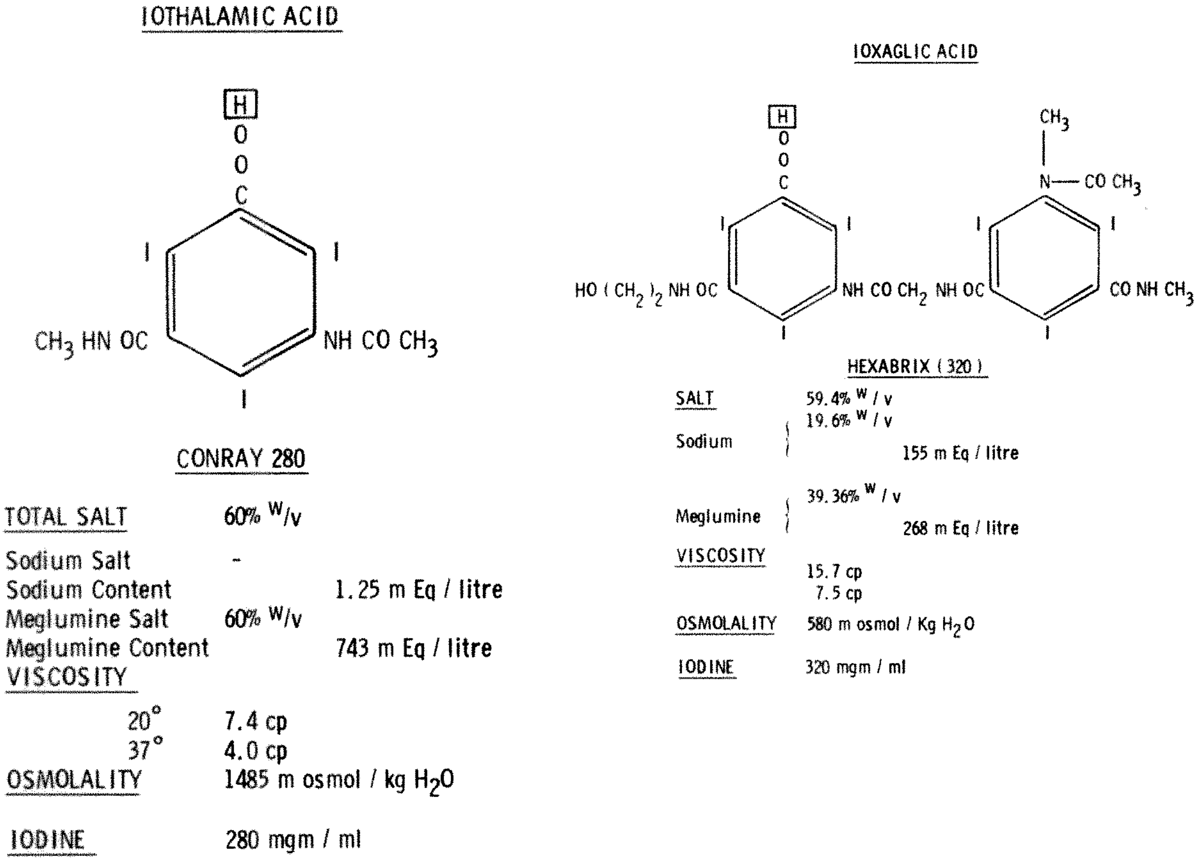
TABLE II

Reaction of patients to each injection of contrast medium

33 Patients	Response				Total injections
	Hot	Warm	Slightly warm	Nil	
Conray 280 (meg. iothalamate	71	7	0	0	78
Hexabrix 320 (sod. & meg. ioxaglate)	7	47	24	0	78

Arteriography was performed under local anaesthesia using the Sheldon needle–cannula assembly. Most of the injections were made into the terminal segment of the common carotid artery, some were made into the origin of the internal carotid artery; no injections were made selectively into the external carotid artery. Injections of the two contrast media were made without moving the cannula. No indication was given to the patient that two contrast media were being used. The two contrast media were injected in randomized order and not alternately, but a count made at the end of the clinical trial showed that 78 injections had been made of each of the two contrast media.

One or other of the two contrast media (8 ml warmed to 37°C) were administered by hand injection taking 1.5 sec. Immediately after each



CONRAY 280

TOTAL SALT 60% W/v

Sodium Salt -

Sodium Content 1.25 m Eq / litre

Meglumine Salt 60% W/v

Meglumine Content 743 m Eq / litre

VISCOSITY

20° 7.4 cp

37° 4.0 cp

OSMOLALITY 1485 m osmol / kg H_2O

IODINE 280 mgm / ml

HEXABRIX (320)

SALT 59.4% W / v

Sodium 19.6% W / v 155 m Eq / litre

Meglumine 39.36% W / v 268 m Eq / litre

VISCOSITY 15.7 cp 7.5 cp

OSMOLALITY 580 m osmol / Kg H_2O

IODINE 320 mgm / ml

Fig. 1.

Comparison of physico-chemical data of Conray 280 and Hexabrix 320.

injection, the patient was asked by the staff nurse in attendance if the injection had produced any discomfort. As the main and often the only discomfort was that of a sensation of heat or warmth in the carotid artery territory, the degree of subjective heat was used as the basis of the assessment of discomfort (see under Discussion). The patient was asked to grade the degree of heat as—No heat (0), slightly warm (1) warm (2) or hot (3). Any other relevant symptoms were recorded.

CONTRAST MEDIA

The physical and chemical data are presented in Fig. 1. Conray 280 is the contrast medium which we currently use for carotid angiography. It is a 60% w/v solution of the meglumine salt of iothalamic acid. This acid is a mono-basic acid and consists of a single benzene ring to which are attached 3 atoms of iodine. One molecule of the salt in solution dissociates into one cation (meglumine) and one anion (the iothalamate radicle containing 3 atoms of iodine). Conray 280 contains 280 mg iodine/ml, and has an osmolality of 1485 mosmols/kg water.

Conray 280 is the registered name of May & Baker Ltd. (Dagenham, Essex).

Hexabrix is the contrast medium under investigation. It is a 59.4% w/v solution of a 2:1 mixture of the meglumine and sodium salts of a newly synthesized acid—ioxaglic acid. This acid is a mono-acid dimer and consists of two benzene rings to which are attached six atoms of iodine. One molecule of the salt in solution dissociates into one cation (sodium or meglumine) and one anion (the ioxaglate radicle containing six atoms of iodine).

Hexabrix contains 320 mg iodine/ml and has an osmolality of 580 mosmols/kg water, *i.e.* about 40% that of Conray 280, despite the 14% increase in iodine content of Hexabrix.

Hexabrix is the registered name of Laboratoire Guerbet (Paris) who synthesized ioxaglic acid.

RESULTS

The results of the patients' answer to the nurse's enquiry regarding any discomfort following each injection are presented in Table II. Each patient reported a remarkably similar response to each injection of the same contrast medium. It was therefore possible to construct Fig. 2. showing how each patient compared the subjective response to the two media.

Table II demonstrates that as many as 71 out of 78 injections of meglumine iothalamate were reported as "hot" and the other 7 as "warm". Following injection of sodium and meglumine ioxaglate, only 7 out of 78 injections were reported as "hot", 47 as "warm" and 24 as "slightly warm". No injection of either product was made without producing some sensation of warmth.

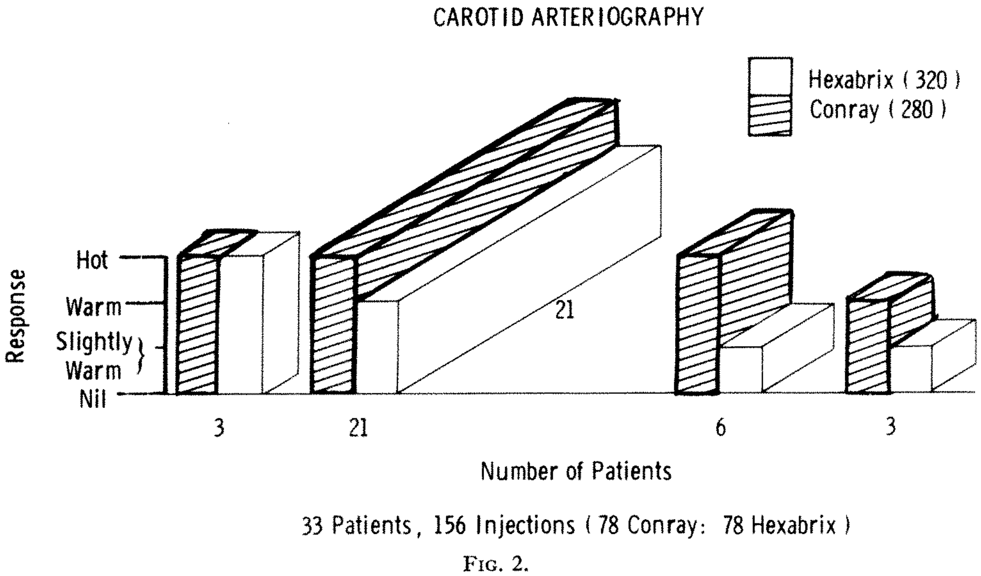


FIG. 2.

Number of patients on x-axis and represented by "oblique depth" of the blocks.
Degree of heat on y axis.
30 patients (21+6+3) preferred Hexabrix 320.
3 patients did not prefer either product.
0 patients preferred Conray 280.

No patient made a spontaneous vocal objection to any injection, or moved because of the discomfort of the injection.

Figure 2 demonstrates that no patient out of the 33 examined preferred meglumine iothalamate to sodium and meglumine ioxaglate. Only three patients reported the same degree of heat from the two media. All of the other 30 patients preferred the ioxaglate as they considered it gave a significantly lesser degree of uncomfortable warmth.

The quality of the cerebral angiograms made with the two different contrast media could not be reliably distinguished from each other, although the ioxaglate solution contained 14% more iodine than the iothalamate.

Discussion

Assessment of discomfort

In a trial period before this investigation was started, an attempt was made to encourage the patient to differentiate the sensation of pain from that of heat following contrast medium injection into the carotid artery. Few could do so with confidence or reliability. Few patients complained of pain as distinct from heat sensation.

During this trial period we also encouraged the patients to score the degree of discomfort, heat or pain on a 100 mm analogue scale as suggested by Ohnhaus and Adler (1975) and Tillman *et al.*, (1979). We found that several patients undergoing carotid angiography found it difficult to co-operate to that extent. We therefore adopted a verbal assessment of the degree of heat experienced by the patients as the main criterion of patient discomfort.

The degree of warmth was graded—absent (0), slightly warm (1), warm (2) and hot (3). It is thought that this grading has proven reliable as the patients consistently gave the same evaluation grade to different injections of the same solution although they were unaware of which medium had been injected.

The contrast media

The two contrast media used in this trial differ from each other in many parameters as is shown in Fig. 1.

The iodinated anions are completely different: iothalamate has a single benzene ring to which are attached three atoms of iodine; ioxaglate has two benzene rings to which are attached six atoms of iodine.

The cation content differs both qualitatively and quantitatively: Conray 280 has only meglumine ions (743 m Eq/litre) (with a negligible sodium ionic content (1.25 m Eq/litre) due to the added buffer). Hexabrix contains both meglumine ions (268 m Eq/litre) and sodium ions (155 m Eq/litre). The manufacturers of Hexabrix (Laboratoire Guerbet) selected this combination of cations in Hexabrix in order to combine most effectively the low toxicity of meglumine with the low viscosity and the physiological "requirement" of sodium ions.

The osmolality of Hexabrix (580 mosmols/kg water) is much less than that of Conray 280 (1485 mosmols/kg water). This is because both ioxaglic and iothalamic acids are mono-basic acids, but the former contains two benzene rings and six atoms of iodine whilst the latter contains only one benzene ring and three atoms of iodine. It is this feature of markedly lower osmolality that is probably the reason for the much improved patient tolerance of Hexabrix. Hyperosmolar solutions cause vasodilatation and a considerable increase in peripheral blood flow which accounts for much of the discomfort.

The iodine content of the two contrast media is different. Hexabrix contains 320 mg iodine/ml whilst Conray 280 contains 280 mg I/ml. The iodine content of Hexabrix is therefore 14% (*i.e.* 320–280/280 × 100) greater than that of Conray 280. At first we proposed diluting the Hexabrix to provide 280 mg I/ml to permit a comparative trial of two contrast media of equal iodine content. The manufacturers however at present propose to advocate Hexabrix 320 for cerebral (and other) angiographies, and it was therefore considered that the most clinically relevant comparison was to compare Hexabrix 320 and Conray 280 (our currently preferred contrast medium) for cerebral arteriography, despite the higher iodine concentration of the former.

Despite this considerable "handicap", as many as 30 out of 33 patients preferred Hexabrix 320 to Conray 280 (Fig. 2), as the former gave significantly less uncomfortable sensation of warmth (Table II).

If the Hexabrix had been diluted to the same iodine content of 280 mg/ml as Conray 280, it is quite likely that there would have been an even greater patient preference for Hexabrix. As well as reducing the iodine content by 12.5% (*i.e.* 320—280/320 × 100), this dilution would have reduced the osmolality by 12.5% and it is osmolality that is probably the major factor in causing the uncomfortable sensation of heat on injection of contrast medium.

Previous assessment of Hexabrix for cerebral angiography

Gonsette (1978) found Hexabrix (320) to be much better tolerated for carotid angiography than a conventional monomeric contrast medium—Vasobrix 32— (meglumine and mono-ethanolamine ioxithalamate 320 mg I/ml). Out of 89 patients receiving Hexabrix, four complained of heat and two complained of pain—an incidence of 7%. This compares well with three out of our 33 patients—9% who complained of feeling "hot" (as opposed to warm) after Hexabrix intra-carotid injection. Gonsette (1978) found that thermography demonstrated much more rise in facial skin temperature after Vasobrix 32 intra-carotid injection than after Hexabrix.

Gonsette (1978) also demonstrated that in guinea pigs, ioxaglate ions (Hexabrix) cause much less damage to the blood-brain barrier than conventional monomeric media. Concentrations as high as 41% of sodium ioxaglate could be injected into the carotid artery without inducing demonstrable lesions of the blood-brain barrier. Various conventional monomeric contrast media produced these lesions when injected in concentrations above 23–34%. It is very likely that in the clinical situation, Hexabrix is less deleterious than current monovalent salt contrast media in terms of disturbance of intra-cerebral haemodynamics and capillary permeability (the blood-brain barrier) as well as providing improved patient subjective acceptability.

Femoral arteriography

Femoral arteriography with conventional monomeric contrast media is usually considerably more painful than is intra-carotid injection using the same concentration of contrast medium. Patients undergoing femoral arteriography with conventional media often suffer pain as well as severe heat in the leg, sufficient to cause movement of the leg and a vocal protest. These severe reactions are rarely seen in carotid arteriography: they did not occur in our 33 patients. In the 30 patients in whom we have compared Hexabrix 320 with Conray 280 for femoral arteriography, there has been a remarkably improved tolerance of the former product, despite its 14% higher iodine content. No patient complained of severe heat, pain, moved or cried out after Hexabrix injection into the external iliac artery. Holm and Praestholm (1979) and Tillman *et al.* (1979) similarly found a greatly improved tolerance of Hexabrix compared with conventional salts (diatrizoate and ioxithalamate) for femoral arteriography.

The improvement of patient acceptability of Hexabrix is even more marked in (the more painful) femoral than in carotid arteriography. In carotid arteriography, there is in addition, the major clinical advantage of markedly less damage to the cerebral blood-brain barrier than is caused by current contrast media.

CONCLUSION

It is concluded that a new mono-acid dimeric salt solution—sodium and meglumine ioxaglate (Hexabrix) is much better tolerated by the patient and causes less damage to the blood-brain barrier than do currently used monomeric contrast media in carotid arteriography.

ADDENDUM

Since this article was written, the author has performed another 100 percutaneous angiographies of various arteries using Hexabrix 320 under local anaesthesia. The following are our conclusions.

1. The results reported in the above paper are fully confirmed.
2. There was no untoward adverse reactions attributable to the contrast medium.
3. Hexabrix is of the greatest (subjective) advantage to the patient in the uncomfortable or painful arteriographies (*e.g.* iliac, femoral, external carotid, hand arteriography). No patient undergoing iliac or femoral arteriography with Hexabrix complained of pain, uttered a vocal protest or moved during or following the injection. These adverse responses occur in about 30% using Conray 280 or Urografin 60. Because of the much improved patient acceptance of Hexabrix, local anaesthesia may be used in many patients in whom general anaesthetic may have been preferred if conventional monomeric salts (*e.g.* Conray, Urografin) had been used.
4. Major expense (literally millions of pounds) is incurred in the sophisticated chemical synthesis and the assessment of the new low osmolality contrast media, of which Hexabrix is one example. The author considers that these products will soon prove to be the contrast media of choice for all angiographies. It is earnestly hoped that the cost to the consumer of these new more expensive contrast media will not be so great as to inhibit their adoption as the angiographic media of choice.

ACKNOWLEDGMENTS

The author wishes to thank the patients who participated, the staff of the X-ray Department of Fulwood Annexe of The Royal Hospital, Sheffield, Mr. A. Crichton of May & Baker Ltd., Dagenham, Essex and Monsieur Jean Lautrou of Laboratoire Guerbet, Paris, and Mrs. V. Morris who kindly typed the manuscript.

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Book reviews

Late Biological Effects of Ionizing Radiation. Proceedings of a Symposium, Vienna, March 13–17, 1978. Vol. I, pp. 548, 1978 (IAEA Vienna). $44.00.
ISBN 92-0-010678-1.

This first volume of some 550 pages covers the papers and discussion of sessions concerned mainly with the evaluation of data on late effects on irradiated human populations. These include the atomic bomb survivors, patients receiving medical exposures, and also routinely or accidentally exposed radiation workers.

It is the controversy presented in evaluation of data from the first and third of these groups, which indicates the uncertainties in our knowledge of the dose-response relationships for late effects following low doses accumulated at low dose rates.

Several papers indicate lines for further investigation, for example the paper "Studies on Persons exposed to Plutonium" (Voelz *et al.*, IAEA-SM-224/508) concludes that although "the present study has yielded no evidence of excessive mortality among 224 male plutonium workers, a more extensive study is required". Moreover, this paper, as well as two separate analyses of the Hanford workforce, indicate an unexpected increase in incidence of carcinoma of the pancreas. This surely indicates that for late radiation effects we do not yet know what we should look for as a radiation related lesion, let alone how much of it to expect.

This volume contains useful data also on late effects of high doses of radiations as used in therapy, and indicates the type of non-stochastic effects, e.g. on blood vessels, which ICRP have now included in their recommendations for dose-limits (ICRP 26). There are reports of non-stochastic effects on the skin and on the eye which call into question the revised dose-limits for these tissues in ICRP 26.

Whilst this is an essential reference source for those involved in assessing acceptable levels of radiation exposure for man, it suffers from the disadvantages of many symposia publications. The papers have not undergone peer review, or editing, which results in inaccurate references and the inclusion of meaningless or misleading statements in the discussion. The book needs to be read, but to be read with these caveats in mind.

Patricia J. Lindop.

Health and Medical Physics. Proceedings of the International School of Physics Enrico Fermi, Course LXVI, Varenna, Italy, 1975. Edited by J. Baarli. pp. xvi+535, illus. 1977 (North-Holland Publishing Co.), $89/D.fl.200.
ISBN 0 7204 072 8

For a number of years, the Italian Physical Society has organized courses on a wide variety of topics at the Villa Monestaro on the shore of Lake Como. This beautiful venue has proved ideal, both in respect of its "atmosphere" for intellectual exercise, and in its capacity to attract world authorities to participate as teachers. Fortunately, the proceedings of these courses are subsequently published.

The present volume contains the proceedings of the sixty-sixth course in the "Enrico Fermi" series, a course directed by J. Baarli from CERN. Although entitled "Health and Medical Physics", this volume is primarily devoted to radiological topics.

The volume is divided into five principal areas:

(i) "dosimetry", covering both radiation beams and radionuclides;
(ii) "methods of medical diagnostics", covering diagnostic radiology (including CAT), nuclear medicine, ultrasonics and thermography;
(iii) radiotherapy, including treatment planning;
(iv) radiation protection, covering the needs of hospitals, reactors and industry;
(v) computer applications, in radiotherapy planning and in medicine generally.

One need only mention that amongst the twenty authors drawn from seven countries, in addition to the Director one finds such well-known names as J. R. Cunningham, J. R. Greening, B. Larsson, J. B. Massey, R. Oliver, N. G. Trott. . . to appreciate the standing of the contributors.

This volume draws together a wide range of basic radiological physics, providing the reader with an excellent introduction to each topic. It should prove particularly valuable to relative newcomers to the profession, or indeed to anyone entering any new area within the field. It is unfortunate that the price may prove a significant deterrent.

W. A. Jennings.

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The normal metacarpal index

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ABSTRACT

Normal values for the metacarpal index (MCI) in British children and adults have been determined. In infancy before the appearance of the metacarpal epiphyses the index is constant up to about two years of age (5.2 in males and 5.5 in females). During childhood the index rises to reach a peak at about 16 years, and then falls slightly during adult life. The curves produced are almost identical to those previously found in black children, and one set of values may be used for children of either ethnic origin. The left hand should be used to calculate the MCI, and the results expressed as either below the mean for age, or in terms of percentile for age above the mean. Curves are presented showing percentile values. No attempt should be made to produce a clear distinction between normal and abnormal indices, but the percentile value used in conjunction with other clinical findings in the assessment of Marfan's syndrome and other skeletal conditions associated with arachnodactyly.

Arachnodactyly is found in several conditions, the most common of which is Marfan's syndrome. In some people it is seen as an isolated finding with no other evidence of disease. Long slender fingers may be obvious clinically, but it is useful to have an objective measurement by which arachnodactyly can be assessed. The metacarpal index (MCI) was first measured in 1960 (Sinclair *et al.*), and since then normal ranges have been determined in adults (Parish, 1960, 1966; Eldridge, 1964) and in infants (Joseph and Meadow, 1969).

Many patients with arachnodactyly first present during childhood, and normal values are required for this age group. Standards have recently been established in Jamaican children (Walker and Ashcroft, 1978), and the present study was undertaken to determine normal ranges in British children. The MCI in adults was also re-assessed, and changes during adult life examined.

SUBJECTS

Children who have had their bone age determined at Bristol Children's Hospital were chosen as the source of radiographs up to the age of skeletal maturity. In all cases the left hand had been X-rayed for bone age assessment by the methods of either Elgenmark (1946) or Tanner *et al.* (1962; 1975). The indication for the bone age measurement was not considered. Films were accepted for the survey if there was no evidence of disease affecting the index, middle, ring or little finger metacarpal bones. There were 1470 males below the age of 16 years, and 1274 females below 15 years.

The MCI in adults was measured in the left hand mainly in patients attending the Accident and Emergency Department of Bristol Royal Infirmary. Some films were also obtained in patients from the Orthopaedic and Rheumatology Outpatient Departments. Radiographs were rejected if there was any disease present which might influence the dimensions of the metacarpal bones. The MCI was measured in 246 males and in 262 females.

The great majority of both children and adults were white, although some subjects of other ethnic origins were included.

METHODS

The MCI in adults and children with ossified metacarpal epiphyses was determined using the method described by Walker and Ashcroft (1978). In infants and young children the epiphyses of the metacarpal heads were included in the length only if all four epiphyses were visible. If all four were not ossified, then the length of each metacarpal was measured as the longest length from the base to the most distal part of the metaphysis of each bone. This varies from the method of Joseph and Meadow (1969), who included any epiphysis which was ossified, even if they were not all visible.

In children it was considered that the MCI might be influenced by the bone age, and the index was therefore calculated separately for those with retarded, normal and advanced bone ages. The 25th and 75th percentile values were used to separate these groups.

RESULTS

The mean MCI and standard deviation was determined for each sex and age group. For children without ossified epiphyses the results are shown in Tables I and II. The mean MCI for males up to 27 months of age is 5.18, and for females up to 21 months is 5.47.

The results for children with epiphyses and for adults are shown in Tables III and IV. There were approximately equal numbers of subjects with

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TABLE I
The metacarpal index (MCI) in males before ossification of the metacarpal epiphyses

Age in months	Number of subjects	Mean MCI	Standard deviation
0–2	30	5.28	0.44
3–5	32	5.22	0.41
6–8	49	5.22	0.54
9–11	40	5.13	0.44
12–14	51	5.26	0.40
15–17	45	5.04	0.42
18–20	43	5.14	0.49
21–23	43	5.19	0.45
24–26	24	5.17	0.48
27–29	18	5.42	0.55
30–32	12	5.62	0.55
33–35	13	5.61	0.59

TABLE II
The metacarpal index (MCI) in females before ossification of the metacarpal epiphyses

Age in months	Number of subjects	Mean MCI	Standard deviation
0–2	36	5.54	0.52
3–5	35	5.48	0.48
6–8	37	5.43	0.56
9–11	44	5.42	0.50
12–14	39	5.38	0.58
15–17	38	5.47	0.60
18–20	26	5.39	0.43
21–23	15	5.77	0.57
24–26	21	5.74	0.63
27–29	8	5.88	0.58
30–35	7	5.64	0.42

retarded and advanced bone age in each sex. When these children are compared with those with normal bone age, there is very little difference within each age group. Using Student's "t" test, there was no significant difference at any age in females ($p < 0.05$ at all ages), while in males there was significance only in 7-year-old and 13-year-old children with advanced bone age ($0.02 < p < 0.05$).

Discussion

In infants before ossification of the metacarpal epiphyses the MCI falls slightly with growth until about two years of age; this fall is very small, and the mean values regardless of age may be used as the normal index up to 27 months in males (MCI=5.2), and up to 21 months in females (MCI=5.5). Joseph and Meadow (1969) found that the MCI increased slightly with age during the first two years of life in their series of 50 children assessed each six months; this discrepancy is perhaps due to the fact that they included any epiphysis which was visible in the length of the metacarpal, even if all four were not ossified. If this is taken into account, then the present survey correlates well with that of Joseph and Meadow.

After about two years the MCI begins to rise rapidly. This rise is at the same rate as in those children with ossified epiphyses, and it is probable that growth at the metaphyses mainly accounts for this.

TABLE III
The metacarpal index (MCI) in males with ossified epiphyses (SD=standard deviation)

Age in years	All subjects			Retarded children			Normal children			Advanced children		
	No.	MCI	SD	No.	MCI	SD	No.	MCI	SD	No.	MCI	SD
1	13	5.44	.73	1	4.82		5	5.17	.84	7	5.72	.62
2	64	5.90	.62	13	5.90	.38	38	5.90	.68	13	5.91	.72
3	81	6.29	.70	21	6.39	.94	41	6.21	.60	19	6.37	.60
4	84	6.48	.68	28	6.36	.69	33	6.53	.69	23	6.54	.67
5	79	6.85	.64	23	6.75	.65	44	6.82	.59	12	7.13	.77
6	91	6.97	.68	30	6.88	.74	33	7.04	.71	28	6.98	.58
7	86	7.15	.67	21	7.18	.66	42	6.95	.59	23	7.47	.66
8	70	7.12	.63	20	7.12	.56	27	7.20	.57	23	7.03	.77
9	76	7.29	.68	27	7.08	.64	34	7.38	.71	15	7.39	.70
10	63	7.19	.66	20	7.11	.83	20	7.08	.53	23	7.35	.59
11	88	7.42	.74	21	7.55	.71	42	7.33	.80	25	7.49	.70
12	90	7.51	.67	25	7.40	.66	39	7.58	.69	26	7.53	.67
13	67	7.67	.63	21	7.61	.54	23	7.50	.54	23	7.89	.73
14	63	7.83	.77	25	7.57	.66	27	8.06	.90	11	7.83	.48
15	43	7.63	.60	23	7.60	.61	15	7.49	.47	5	8.20	.65
16–19	56	7.84	.60									
20–29	54	7.60	.62									
30–39	49	7.56	.56									
40–49	24	7.41	.42									
50–59	31	7.47	.61									
60–69	22	7.41	.57									
70–79	9	7.13	.93									

TABLE IV

The metacarpal index (MCI) in females with ossified epiphyses (SD = standard deviation)

Age in years	All subjects			Reatarded children			Normal children			Advanced children		
	No.	MCI	SD	No.	MCI	SD	No.	MCI	SD	No.	MCI	SD
1	58	5.93	.60	13	5.73	.54	38	6.00	.59	7	5.88	.68
2	107	6.15	.67	54	6.07	.61	43	6.18	.74	10	6.34	.64
3	98	6.64	.76	34	6.55	.69	40	6.73	.69	24	6.66	.68
4	68	6.94	.74	26	6.70	.63	28	6.95	.78	14	7.38	.68
5	73	7.17	.67	23	6.94	.67	27	7.25	.60	23	7.31	.69
6	66	7.39	.83	15	7.29	.61	26	7.48	.74	25	7.35	.99
7	67	7.48	.73	18	7.49	.82	21	7.38	.72	28	7.56	.72
8	56	7.74	.69	18	7.63	.81	15	7.76	.57	23	7.82	.68
9	68	7.71	.71	16	7.56	.80	30	7.72	.64	22	7.80	.72
10	74	7.93	.57	14	7.99	.63	24	7.90	.60	31	7.94	.54
11	68	7.95	.71	21	7.76	.78	20	7.90	.48	27	8.13	.80
12	69	8.15	.82	21	7.94	.81	18	8.25	.91	30	8.24	.76
13	50	8.11	.67	27	7.93	.69	16	8.22	.50	7	8.52	.74
14	46	8.12	.77	21	7.81	.71	17	8.18	.73	8	8.82	.57
15	19	8.23	1.09									
16–19	26	8.34	.58									
20–29	44	7.99	.55									
30–39	32	8.14	.47									
40–49	36	8.04	.63									
50–59	65	7.88	.57									
60–69	43	7.94	.54									
70–79	20	7.98	.43									
80–89	6	7.87	.51									

In children with ossified epiphyses, the combined results regardless of bone age may be used. Although there was selection of subjects, in that only those children who may have had some growth abnormality were referred for bone age assessment, the lack of difference in the MCI between children with retarded, normal and advanced bone age indicates that the bone age has little effect on the MCI. When these combined figures are used, the MCI is seen to rise rapidly in the early years, and to level off as skeletal maturity is approached. These measurements are almost identical to those found previously in Jamaican children (Walker and Ashcroft, 1978), suggesting that black children have metacarpals of the same proportions as white children, and that there are no ethnic differences.

The figures obtained in adults are slightly lower than those in Jamaican adults, although this is largely the result of a greater proportion of young adults in the Jamaican series; they are, however, higher than those obtained by other workers (Sinclair *et al.*, 1960; Parish, 1960, 1966; Eldridge, 1964; Harris *et al.*, 1973). The differences produced by differing methods of measurement of the lengths of the metacarpals do not account entirely for this discrepancy. The present study may well include some subjects, both children and adults, with syndromes in which arachnodactyly is a feature, and no attempt has been made to exclude those with clinically long fingers, whereas this may have been done in the previous studies. Sinclair *et al.* (1960) used only the right hand, which has been shown by Parish (1966) to give a slightly lower MCI than the left hand; also, they do not state the age or sex of their control subjects, and may have included some children in the series, thereby lowering the index.

Various methods have been used to determine the upper limit of the normal MCI. Sinclair *et al.* (1960) used the gap between their measurements for normals and those with Marfan's syndrome (normal up to 8.1, equivocal 8.1–8.4, arachnodactyly above 8.4), although some doubt has been cast on the significance of these figures (McKusick, 1972). Similarly, Eldridge (1964) took the highest figure of his non-Marfan subjects as the upper limit of normal (8.8 in males, 9.4 in females, mean of both hands). Parish (1966) used three standard deviations above the mean as the dividing line (8.4 in males, 9.2 in females), but stated that this must be expected to include some normals in the arachnodactyly range; he also found some patients with Marfan's syndrome who had an MCI below the three standard deviation level.

Workers have also used different measurements in clinical practice. For example, Emanuel *et al.* (1977) used a value of 8.4 to define arachnodactyly, while

Payvandi *et al.* (1977) chose an index of 8.1 as the lower limit of their abnormal cases. Neither of these series took the age or sex of the patients into account.

In most clinical measurements there is a wide range of normal, and it is not possible to give a single measurement which separates normal from abnormal. The percentile method is now used for many physical parameters, including height, weight and bone age. It is suggested that the MCI should also be expressed in terms of percentile for age, which makes it easy to relate an individual reading to the normal population. In infants without ossified epiphyses, mean and percentile levels are given in Table V. Curves for older children and adults are shown in Fig. 1 and 2.

In patients with borderline arachnodactyly, serial measurements can be made and compared with normal percentile charts. This may be of value in doubtful cases of Marfan's syndrome, when the index might be expected to rise more rapidly than in the normal. This is suggested by two patients quoted by Sinclair *et al.* (1960) in whom the rise in MCI was very rapid over three years; in one of these the initial measurement was on the 70th percentile, whereas the final index was considerably above this.

TABLE V

MEAN AND PERCENTILE VALUES FOR THE METACARPAL INDEX IN INFANTS BEFORE OSSIFICATION OF THE EPIPHYSES

	Males Birth to 27 months	Females Birth to 21 months
Mean	5.2	5.5
75th percentile	5.5	5.8
90th percentile	5.7	6.1
97th percentile	6.0	6.4

It appears logical to select the left hand in the estimation of the MCI. The left hand is used to measure the bone age by the methods of Elgenmark (1946), Tanner *et al.* (1962; 1975), and Greulich and Pyle (1966), and is therefore frequently X-rayed in children with suspected skeletal syndromes.

Some explanation must be given for changes in the MCI with age. In infancy the shape of the metacarpals remains roughly constant, and the MCI shows relatively little change until about two years of age. Once the epiphyses become visible, the length increases proportionally more than the width, mainly because maximum growth takes place at the epiphyseal plate. Additionally, as growth advances, a greater proportion of the epiphysis ossifies, until by the age of skeletal maturity the epiphysis is entirely ossified except for the articular cartilage.

It is not easy to explain why the MCI should fall during adult life. The fall is small, and is less than one standard deviation in both males and females. No previous reports have studied the change in MCI in adults, although when Harris *et al.* (1973) found that their control subjects had a slightly lower MCI than those of Parish (1966) they reported that their group "was older (than Parish's) which would tend to reduce their MCI"; however, they produced no evidence to support this statement. It seems unlikely that in the absence of joint disease the length of the metacarpals would be reduced in older age groups; it may be that the interossei muscles inserted into the shafts of the metacarpals produce a gradual increase in the width of the bones over many years. In an attempt to assess this, the lengths and widths were studied separately in adults, but no significant change in either length or width was found at different ages.

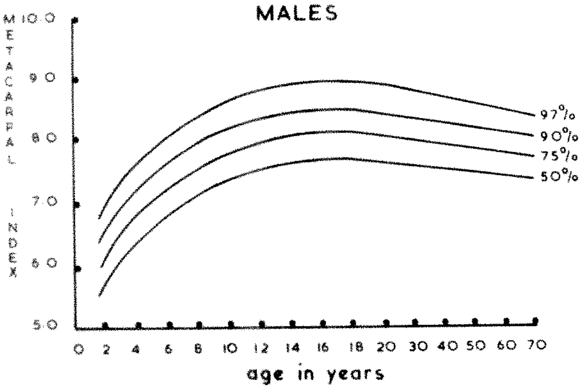

FIG. 1.

Mean and percentile curves for the metacarpal index in male children and adults.

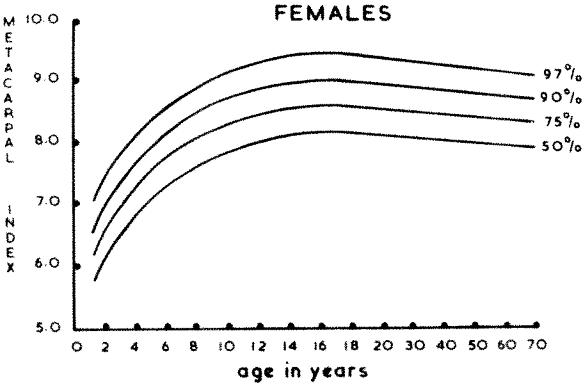

FIG. 2.

Mean and percentile curves for the metacarpal index in female children and adults.

ACKNOWLEGMENT

The author wishes to thank the late Dr. I. R. S. Gordon for his kind help and advice in the preparation of this paper.

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Book reviews

Cancer: Science and Society. By John Cairns, pp. 199, 1978 (W. H. Freeman and Company; Reading, Berks; San Francisco, U.S.A.) Hardback £6·20/Soft cover £2·90. ISBN (Hardback) 0-7167-0098-0/(soft cover) 0-7167-0097-2.

This is not a book for radiotherapists since the author has "gone out of his way to avoid discussing the accepted treatments and probable outcome for each type of cancer". Despite this disclaimer, I feel that the average reader may be left with an unduly pessimistic picture of the overall results of modern cancer therapy.

The book is addressed to two classes, the general public and students who may be considering a career in cancer research. It is notoriously difficult to write popular science, "and every attempt is a new start, and a different kind of failure". The author is aware of the difficulty and suggests that those lacking a scientific background skip chapters 7 and 8 on Experimental Cancer Research. Perhaps I am too pessimistic, but I doubt if chapter 6 on Molecular Genetics, or even chapter 3 on the Origin and Varieties of Cancer, will be comprehensible to the hypothetical man in the street.

This book will certainly be of great interest to students of the biological sciences, and perhaps it should be compulsory reading for those concerned with the strategy of cancer research.

The author casts doubt on the value of early treatment, screening and, by implication, cancer education. This is certainly very stimulating, although it may be a little confusing for the general public who have been taught the vital importance of "catching the disease in time".

The reference to radiation carcinogenesis on pages 105–106 is misleading and could have been omitted.

O. C. A. SCOTT.

Advances in Neurosurgery. 6. Treatment of Hydrocephalus Computer Tomography. Edited by R. Wullenweber, H. Wenker, M. Brock, M. Klinger, pp. xxix+230 1978 (Springer-Verlag, Berlin, Heidelberg, New York) DM64/$35.20. ISBN 3-540-09031-2.

This book contains the edited proceedings of the joint meeting of the German, Dutch and British Societies of Neurological Surgeons, which took place in May, 1978. It is divided into three sections. The one of main interest to radiologists is on computer tomography and mainly deals with diagnostic errors and difficulties. While it is always interesting to learn from the trials of others, the difficulties recorded are in general well known to radiologists working in the field. There is a very good contribution from Newcastle (McAllister, Hankinson and Sengupta), which includes experience with metrizamide cisternography, and another by Polkey correlating CT appearances with the pathology in anterior temporal lobectomy specimens removed for intractable epilepsy.

One section dealing with complications of shunt operations performed for hydrocephalus is important background reading but contains little of specific radiological interest.

The final section containing free presentations on more general subjects includes one interesting paper by Overbeck discussing operative angiography. He has used the procedure with satisfactory results in 80 cases and illustrates the excellent films produced using fine a focus tube and 70 mm camera.

The editing is good and the book is well produced with illustrations of high quality.

B. E. KENDALL

1977, *British Journal of Radiology*, *50*, 792–795

A comparison of two techniques of detecting vesico-ureteric reflux

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(*Received March 1979*)

Abstract

Indirect voiding radionuclide cystourethrography has been compared with micturating cystourethrography in 57 children with urinary tract infections. A quasi-quantitative technique utilizing a mini-computer to optimize the images from the gamma camera has been shown to be at least as sensitive as conventional radiological techniques but to give these results without catheterization, at a lower radiation dose and at lower cost.

Micturating cystourethrography (MCU) is neither a safe nor a pleasant investigation. Nevertheless it is generally accepted as the standard technique of detecting vesico-ureteric reflux despite its disadvantages. McAlister *et al.* (1974) list 13 possible complications, the commonest of which are that catheterization carries the risk of introducing or reactivating infection, and is frightening for many children. The radiation dose to the gonads is between 1 and 10 rems, depending upon the number of films taken and the duration of fluoroscopy. The probability of detecting reflux is affected by total duration of observation. Reducing screening time, or the number of films taken, in order to minimize radiation has the inescapable consequence of impairing the accuracy of the examination. Reducing the screening current (which can be to some extent offset by the automatic brightness control of the television system) degrades the quality of the image and therefore reduces the chances of detecting small amounts of reflux.

Radionuclide techniques have two theoretical advantages. Firstly the radiation dose is independent of the duration of observation. It is therefore possible to record continuously—equivalent to screening continuously for an indefinite period. Secondly it is possible to use intravenously administered tracers, thereby avoiding vesical catheterization. Published reports of the sensitivity of indirect voiding radionuclide cystourethrography (IVRC) compared to that of the MCU are contradictory (Conway and Kruglik, 1976; Hedman *et al.*, 1978).

We have developed a technique of IVRC which we believe to be at least as sensitive as the MCU, but which results in a much lower absorbed radiation dose (about 50 millirem to the gonads), eliminates the need for catheterization and is easily reproducible.

Selection of Patients

Children studied were those who presented after acquisition of bladder control with bacteriologically proven urinary tract infections according to conventional criteria (Kass, 1956). All boys and those girls with recurrent urinary tract infection were submitted to intravenous pyelography and micturating cystourethrography in line with current practice (Smellie, 1970). Girls with a single urinary infection had either an IVP or radionuclide tests of the kidneys as the first line investigation. Duplicate investigations were only obtained in the presence of an abnormal first line investigation and where it was thought clinically desirable to obtain further information to assist in the child's management.

The IVRC was performed at the end of the function study. As it involved no instrumentation and no increased radiation dose—indeed by minimizing the time radioactivity remained in the bladder it may have somewhat reduced the absorbed radiation dose—the procedure was considered ethically acceptable, even though it was of unproven efficacy.

The records of the Medical Radioisotope Department at the Western General Hospital were used to identify children who had been referred for gamma camera studies of renal function during the period January 1, 1975 to September 30, 1978. The files of the X-Ray departments of the referring hospitals were then searched to identify which of these children had had an MCU. This report is based upon the findings in 57 children in whom both examinations had been performed within three months, usually within six weeks. In no case had any surgery been performed in the interval.

Materials and Methods

Commercial TcDTPA kits were prepared according to manufacturer's recommendations. Various makes were used according to availability.

At the start of the investigation the patient was given at least 250 ml of water or a flavoured drink. After emptying the bladder as completely as possible they were seated in front of a gamma camera equipped with a high sensitivity low energy collimator. An intravenous bolus of 150/μCi/kg of TcDTPA was administered and the data recording system started. Ninety frames, each of 10 sec. duration, were collected. The child was then moved. Boys were asked to stand with their back to the camera and were given a disposable urine collecting bottle. Girls were seated on a specially constructed stool/commode with their backs to the camera. A second series of frames, this time of 5 sec. duration, was collected for as long as necessary. If the child was not able to void they were encouraged to drink more and to try again after an interval. Few children were unable to void within the time available.

Areas of interest corresponding to the kidneys and a "background" area were selected and time/activity curves plotted separately for the initial function study and for the voiding study (Fig. 1). On the latter reflux was identified as a rise in count rate. Confirmation that this rise was due to reflux and not to movement was obtained by inspection of the frames corresponding to the rise in count rate (Fig. 2).

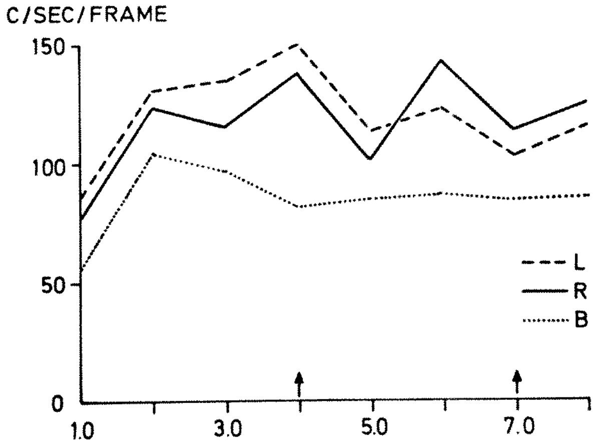

Fig. 1.

Plot of activity in renal areas during voiding. Rise between first two frames is due to movement. The change in count-rate between frames 5 and 6 in the plot from the right kidney is suggestive of reflux.

A display capable of demonstrating at least four frames at a time, and relating the display to the maximum count rate in the whole series of images, rather than to each separate image is essential. Reflux was diagnosed only if an increase in activity in the renal area could be identified both in the images and on the time/activity curves. Fluctuations in count rate due to movement were readily identified by inspection of the images. Reflux was judged as either present or absent. No attempt was made to grade the severity.

Results

The findings are summarized in Table I. Sixty-two of the 114 kidneys studied did not show reflux either on IVRC or on MCU. Reflux was observed during the MCU in 36 of the 52 kidneys (69%) in which reflux was detected by either or both methods, and during the IVRC in 40 (77%).

Discussion

Most previous reports have used either gamma camera pictures or time/activity curves to detect reflux. Time activity curves alone are insensitive, nor do they permit movement to be identified. In a previous (unpublished) study in this department using time/activity curves alone (Table II) reflux was detected in only 18 out of 34 kidneys (53%) whilst 30 (88%) were detected on MCU. The reluctance to diagnose reflux when there was doubt about movement is an important factor in this discrepancy.

TABLE I

		Gamma camera		
		No reflux	Reflux	Total
MCU	No reflux	62	16	78
	Reflux	12	24	36
	Total	74	40	114

TABLE 2.

		Gamma camera		
		No reflux	Reflux	Total
MCU	No Reflux	54	4	58
	Reflux	16	14	30
	Total	70	18	88

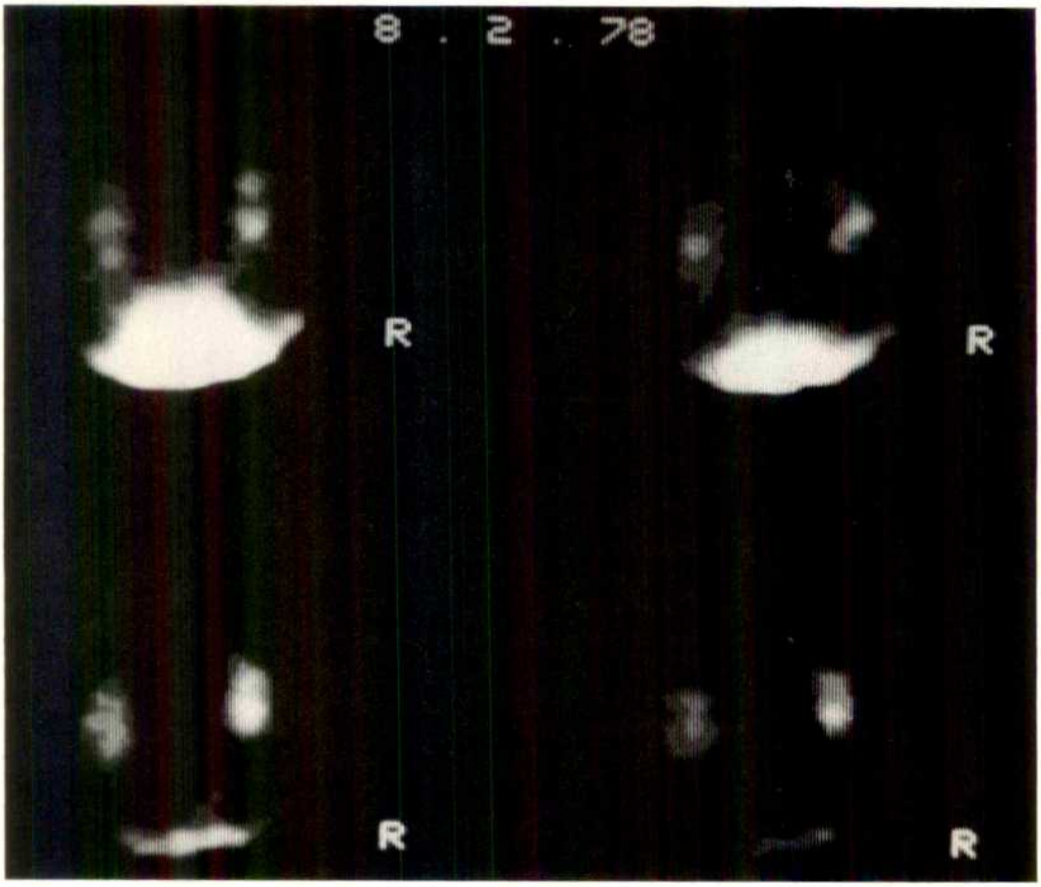

FIG. 2.

Frames 4–7 from which Fig. 1 was derived. Reflux is seen on the right.

Unprocessed gamma camera images are a very insensitive means of detecting often transient and fairly small changes in count rate, which is usually very low in the renal area compared to the bladder. The use of a computer-optimized display, which allows small groups of frames to be inspected and manipulated at leisure, is essential if reflux is to be detected. The evaluation of time/activity curves in association with the images permits differences in count rate to be measured to assess the reality and statistical significance of differences which are apparent in the images, and to distinguish redistribution of radioactivity within the collecting system from true reflux.

It has been found that frames of 5 sec. duration are necessary when detecting reflux. Shorter frames degrade the image because of their poor statistical content. Longer ones minimize transitory differences in count rate, which may be of considerable clinical importance (Figs. 3 and 4).

With this technique reflux was detected slightly more often by IVRC than by MCU. The difference just reaches statistical significance at the 5% level. ($\chi^2=7.7$, $0.01 > p > 0.05$). The apparent superiority of the IVRC is probably due to the much longer observation time possible, amounting to continuous observation before and during voiding, thus giving the best possible chance of detecting transient reflux.

Reflux was transient in over half of the cases in the present series, and this must cast doubt upon the validity of the conventional grading of vesico-ureteric reflux. A transient flash of reflux may easily be missed on fluoroscopy, especially if screening factors are adjusted to minimize radiation. When screening is intermittent and few films are taken, the severity of reflux is likely to be underestimated on the MCU unless the film happens to be taken at the instant when contrast has reached its highest point in the urinary tract.

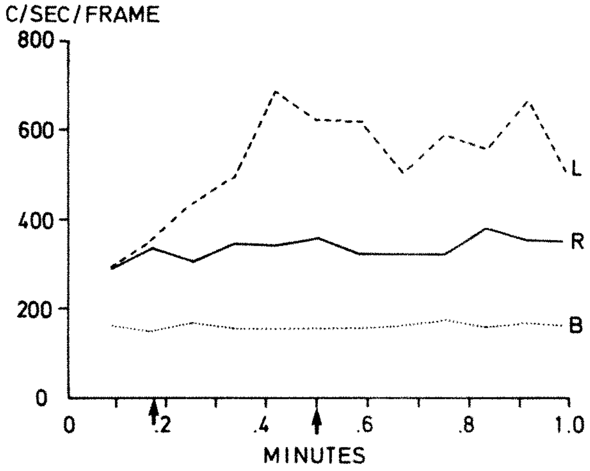

Fig. 3.

Reflux on the left side, also detected on MCU.

The principle disadvantage of the IVRC is the poor anatomical detail compared with the MCU. Structural lesions such as ureterocoeles and diverticula will not normally be detected, and these may also be missed on excretion urography if the concentration of contrast in the bladder is not adequate. Conversely, too high a concentration of contrast during the MCU may also obscure lesions which are not on the periphery of the bladder.

By performing the IVRC at the end of a standard gamma camera renal function examination it is possible to obtain from a single injection information about the separate function of each kidney and the presence or absence of vesico-ureteric reflux. It is also possible to measure glomerular filtration rate if desired. The radiation dose is much lower than from the MCU, and adverse reactions to TcDTPA are extremely rare and very minor when compared with those to radiological contrast media.

Conclusions

Using this technique it is possible to detect and to follow up vesicoureteric reflux without catheterization. The risk and trauma to the child are minimal and the cost is low, especially when it is appreciated that the price of modern radioisotope imaging and data processing equipment is often less than that of conventional X-ray equipment.

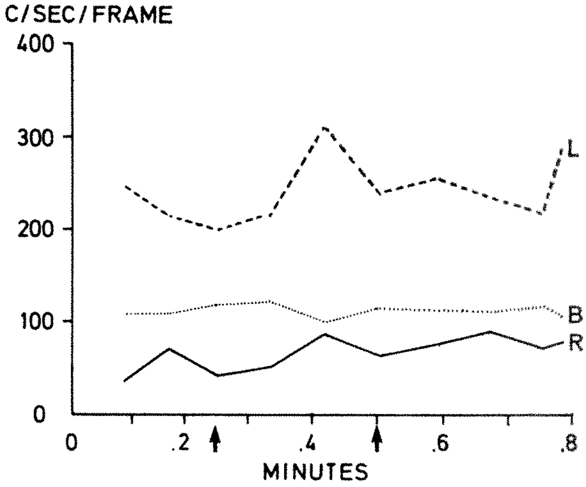

Fig. 4.

Transient reflux, seen only on one frame. Easily missed at MCU, or if longer frame lengths are employed.

Acknowledgments

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A small computer at the radiology reception desk

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(*Received April 1979*)

Abstract
An intelligent terminal has been used at a radiology reception desk to maintain a master patient index and to assist documentation. It also yields valuable management information.

When the King's Lynn Health District agreed to compile and maintain a computer-based master patient index, it was decided to merge the Medical Records and the Radiology Department indexes. The patient records have been transcribed to computer file. Two identical intelligent terminals with printers have been installed, one in the documentation room of the Medical Records Department, and one at the reception desk of the main Radiology Department. The purpose of these terminals is to record information to update the master index. The radiology unit also controls documentation and assists in department management.

General Description (Figure 1)

Seven indexes from the King's Lynn Health District, including the radiology index, were transcribed on to computer file. Naturally, many patients had records on two or more of the indexes, and where possible records were merged and errors reported. The computer file of almost 300000 entries is held on the Regional Health Authority computer (ICL 1900) at Cambridge, and the entire file is reprinted on microfiche every two weeks. A microfiche is a sheet of film (147×115 mm) on which is printed 224 pages of information, each of fifty lines (Fig. 2). Multiple copies of the microfiche make it possible for the master index to be available in several departments. The index is updated from information introduced at the intelligent terminals. The two terminals operate completely independently, and at the end of the day, the information stored on floppy discs (diskettes) is combined and then transmitted to Cambridge via a GPO line. The new data are incorporated into the master index. The RHA prints a list of data which does not match existing information. This error report and a cumulative list of amendments to the last microfiche are sent to the hospital each day.

Registration of a patient at the Medical Records terminal not only creates an input to the master index but also initiates a print of self-adhesive labels to identify documents and specimens. Registration at the radiology terminal creates a master index update, generates a print of labels for film identification and documentation, and yields statistical information which helps in the management of the department.

Details of Radiology Terminal (Figure 3)

The intelligent terminal is a Datapoint 1500 comprising a full keyboard, a 24 line by 80 character video display unit (VDU) and 36k of memory. A dual diskette drive holds two 8 in floppy discs each with a capacity of 250000 characters. One drive operates the daily data diskette, transmitted to the RHA and the other holds a summary of patient attendances and a file of statistical information, both accumulated over a week. The printer, a Centronic 701, prints 60 characters a second using a 5×7 dot matrix. Entry to the system is confined to those authorized by the consultant radiologist in administrative charge. Each user identifies himself/herself by initials and a password. The system is operated during the day by reception staff and after normal working hours by radiographers.

Input to the terminal is achieved via a set of dialogues, called transactions. The user selects a transaction from a list on the screen, and is guided through it by a cursor and appropriate prompts. Certain information is introduced in coded form. Codes are used to identify the source of each request: CAS (Accident and Emergency), IP (Inpatient), OPU (Urgent Outpatient), OPA (Outpatient Appointment), GP (General Practitioner request). The program also holds a table of consultants' names and initials, so that when a patient is referred from IP, OPU or OPA the consultant can be identified from his initials only. (If the patient has been sent by a GP, the GP's name is entered in full and printed on the labels, though not held on the statistics file.) Examinations are identified by a four-digit code designed to facilitate the accumulation of statistics, in particular allowing the automatic derivation of radiographic and radiologists' work units (Fig. 4).

The microfiche are held in an automated fiche reader (Addressograph) which facilitates access to any entry on any fiche in about five seconds.

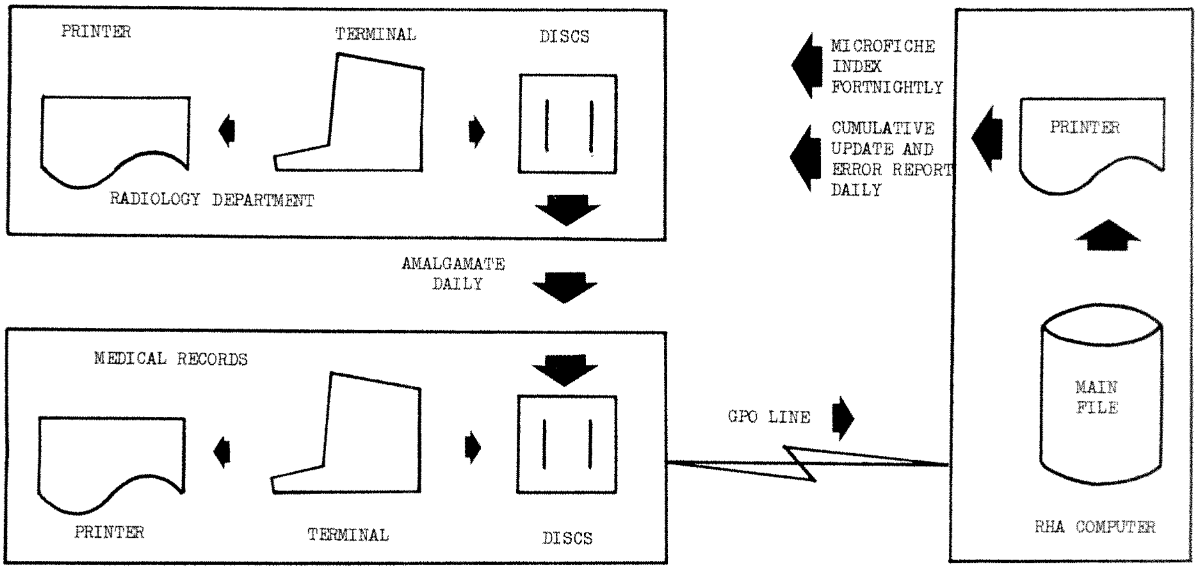

FIG. 1.
A diagram of the King's Lynn master patient index system.

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E.A.R.H.A. COMPUTER SERVICES  KM14/003              KINGS LYNN    TIME 17/30 DATE 25/01/79  PAGE 48
                                                    MASTER INDEX

                                            X RAY
                                            LO-
                       S  DATE              CATION
                       E  OF     HOSPITAL   AND
SURNAME   FORENAME     X  BIRTH  NUMBER     DATE    ADDRESS      DECEASED GP SURNAME     HAA CODE

BRINDLE   MICHAEL J    M  18NO34            KO1.79  HALL LANE,            CHAMBERLAIN
                                                    S. WOOTTON
```

FIG. 2.
An abstract from the fiche illustrating layout of information.

TRANSACTIONS

Seven transactions are available at present:

1. *New patient attendance.* This is used if there is no existing entry on the microfiche, cumulative amendment file or daybook. The program prompts for full patient details. On completion of the transaction an insertion is added to the attendance file and the statistics file is updated as appropriate.

Unless registration takes place after the examination has been performed (at a peripheral department) eight labels are printed. One contains the patient's name and date of birth only and is used to identify the large film packet. The remainder, with full details of the patient, source, examination and date are used to document the large film packet, the film marker, the blank report and copy, the miniature film wallet and the temporary daybook (Fig. 5). The spare label will be used later on a patient location board.

2. *Old patient attendance.* An old patient is one who either has a record of a previous attendance at the Radiology Department, or who has been registered through Medical Records. If that record is no longer accurate it is corrected and where a previous Medical Records entry exists, the opportunity is taken to amalgamate the Radiology and Medical Records information. The computer will automatically include the month and year of this latest radiologic examination, which will subsequently be included on the fiche and may be used to purge the miniature film file at the appropriate time. Labels are printed as for new patient attendances, and similar file updates take place, except that they are in the form of amendments rather than insertions.

3. *Extra statistics.* This transaction is provided to include statistical details such as radiographic units for unco-operative patients or examinations initiated after registration has been completed.

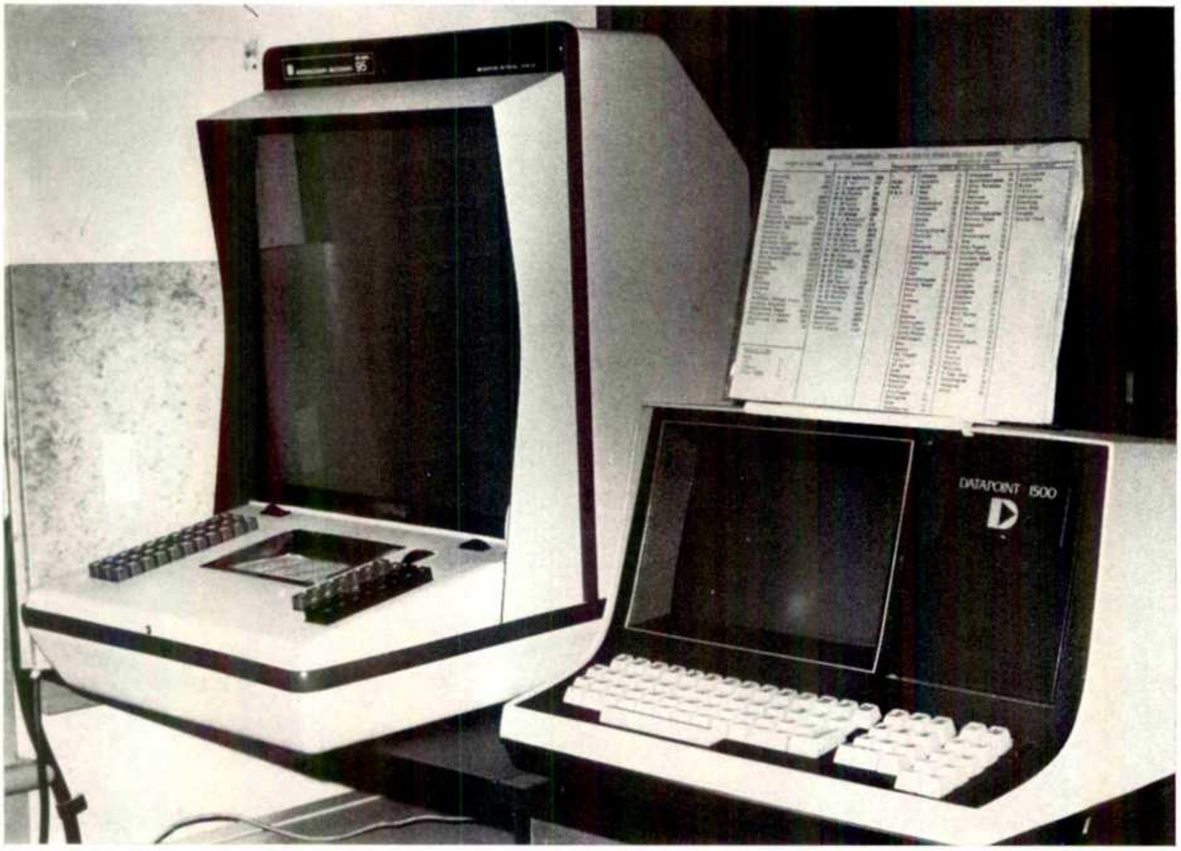


Fig. 3.

Radiology reception desk showing the VDU, examination code and the automated microfiche reader.

4. *Index updating.* The facility to insert, amend and delete index records is provided in order to make it possible to tidy up records on the master index where no patient attendance is involved. These transactions are also used to bring the index up-to-date following a system failure.

5. *Patient enquiry.* This program prompts for the name of the patient and date of attendance. It will then search the weekly patient attendance file and print out the content of any matching record it finds.

6. Ad hoc *enquiry.* The user may interrogate the weekly patient attendance file for any combination of date, source, doctor and examination. The answer may be displayed as a list of matching attendances or as a total number.

7. *Routine statistics.* From the weekly attendance file the following statistical summaries may be obtained:

(a) attendances, examinations and radiographic units (standard, mobile and unco-operative) by source (CAS, IP, OPU, OPA, GP). This may be analysed hospital by hospital or as a grand total. A summary of work performed outside normal working hours is also available.
(b) total examinations performed from IP, OPU and OPA by consultant.
(c) pre-selected examinations by source (CAS, IP, OPU, OPA, GP).
(d) radiologists' work load, group i, ii and iii examinations with derived units.

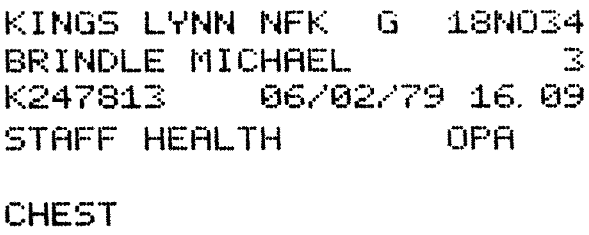
Discussion

The installation was designed to maintain a master patient index, to facilitate the documentation of patients and to provide management information to the consultant radiologist. The original radiology index was small and remarkably accurate while the original medical record indexes were large and contained many errors. When the indexes were combined the errors were, in the main, included and their correction continues to be a major pre-occupation of the Records Department to which we contribute as and when we can. All those concerned

KING'S LYNN DIAGNOSTIC IMAGING EXAMINATION CODE

First digit		Second and third digits				Fourth digit	
—	0	Abdomen	01	Pelvis	51	Arteriogram	1
Right	1	Acjoints	02	Percholangiogram	52	Arthrogram	2
Left	2	Ankle	03	Petrous Bones	53	Biopsy	3
R & L	3	Bone	04	Pregnancy	54	F B Local	4
		Brain	05	Renal	55	Isotopescan	5
		Bronchogram	06	Retrourogram	56	Screening	6
		Calcaneum	07	Ribs	57	Sonar Scan	7
		Cardiac	08	Ring Finger	58	Tomogram	8
		Cspine	09	Sacrum/Coccyx	59	Special Views	9
		Chest	10	Salivary Gland	60	—	0
		Cholecystogram	11	Scanogram	61		
		Clavicle	12	Scaphoid	62		
		Colon	13	Scapula	63		
		Cystogram	14	SCJoints	64		
		Dacryocystrogram	15	Shoulder	65		
		Dental	16	Sialogram	66		
		Diaphragm	17	SIJoints	67		
		Elbow	18	Sinogram	68		
		ERCP	19	Sinuses	69		
		Excreturogram	20	Sklt Survey	70		
		Facial Bones	21	Skull	71		
		Femur	22	Small Bowel	72		
		Foot	23	Spleen	73		
		Forearm	24	Sternum	74		
		Hand	25	Stomach/Duod.	75		
		Hip	26	Tspine	76		
		Humerus	27	Thumb	77		
		Hysterogram	28	Thyroid	78		
		Index Finger	29	Tib/Fib	79		
		Inlet Thorax	30	TMJoints	80		
		Ivcholangio	31	T Tube Chol.	81		
		Knee	32	Urethrogram	82		
		Larynx	33	Venogram	83		
		Ltl Finger	34	Wrist	84		
		Liver	35		85		
		LS Spine	36		86		
		Lung	37		87		
		Mammogram	38		88		
		Mandible	39		89		
		Mastoid	40		90		
		Mid Finger	41		91		
		Myelogram	42		92		
		Nose	43		93		
		Nasopharynx	44		94		
		Oesophagus	45		95		
		Opcholangiogram	46		96		
		Optic Foramina	47		97		
		Orbit	48		98		
		Pancreas	49		99		
		Pelvimetry	50				

Fig. 4.
Four digit code to identify examination and derive work units.



```
KINGS LYNN NFK  G  18N034
BRINDLE MICHAEL         3
K247813    06/02/79 16.09
STAFF HEALTH        OPA

CHEST
```

Fig. 5.
Sample of label produced during registration of patient.

with the operation appreciate the ultimate value of an accurate master index.

The documentation of a patient at the reception desk still takes about two and a half minutes including the search of the microfiche and retrieval of previous films. The discipline imposed by the program has reduced registration inaccuracies to a very low level. When they do occur they are at least found on every document and because of this are often spotted before the error report is published.

The self-adhesive labels produced by the matrix impact dot printer have proved most suitable for film identification by the reflected light photographic method (Kodak X-Omatic) though they would be less satisfactory with transillumination methods. We had hoped to make the daybook obsolete by the use of the patient and *ad hoc* enquiry transactions, but they are rather too slow. A record of transactions may be obtained by replacing the labels with paper in the printer but this interrupts reception work. Consequently we have retained a daybook of adhesive labels. This has proved adequate and has helped to detect errors following the inaccurate input of information such as the date.

The provision of statistical information is very valuable. In this department the amount of non-urgent work (OPA, GP) performed depends upon the demand for urgent work (CAS, IP, OPU) (Brindle, 1978). Each Friday afternoon the weekly statistics are read and the number of appointments to be made for the week after next are deduced. The ability to identify and respond quickly to changes in demand from priority sources is crucial to the success of this form of control. In addition publication of the demand from each source and consultant encourages senior and junior medical staff to avoid inappropriate examinations.

The collection of units of radiographic work required by the authorities has been reduced from a matter of hours to minutes a week. Similarly radiologist work load units can now be obtained so quickly that it was with some regret we learned this information is no longer required (HN(78)137)!

We have suffered very few hardware problems. If there is an equipment failure, the department can still function by reverting to manual procedures. Index and statistical details are recorded retrospectively.

Less satisfactory features of the present system are the inability of the two units to communicate and the impracticability of retrieving and reusing information from previous registrations. A minor inconvenience is the occasional need to consult the fiche, the cumulative update file and the daybook to locate current master index details. In the next phase of the development we plan to overcome these problems with a minicomputer large enough to hold and update on-line two to three years of registrations. This index will be the basis of a comprehensive in- and outpatient system.

Hardware costs have not been included since they are diminishing so rapidly. Initially we had hoped to include in the first phase a reporting system. This did not prove possible but it may be incorporated in the next phase or developed as a separate system based on an independent microprocessor.

Summary

Intelligent terminals have been used successfully to create and maintain a computerized master patient index, to improve the reception and documentation of patients in a Radiology Department and to yield valuable management information. The equipment has proved to be reliable and the system efficient.

Acknowledgments

We are grateful to Mr. A. Cassidy and Mr. P. Westcott and their staff at the RHA Computer Centre, to Mr. W. Jacobs and Dr. R. West for support and encouragement and to Mrs. M. Sansom for typing. We are pleased to acknowledge our debt to Dr. W. B. James (Southern General Hospital, Glasgow).

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Book review

Anatomical Exercises in Computerised Tomography Body Scanning. By Fred C. Shipps, pp. vii+65, 1978 (Charles C. Thomas, Illinois, USA) $22.75.
ISBN 0-398-03746-9

This book sets out to provide an introduction to cross-sectional anatomy as seen during CT scanning of the thorax, abdomen and pelvis. The presentation of the material is simple and clear. Serial scans are illustrated for each part. Alongside each scan there is a diagram of the main anatomical features in colour with a removable labelled overlay to assist identification and learning. Considering that the scans were done using an early scanner the illustrations are good and the essential features are easily seen. The book ends with a quiz which includes some abnormal scans but in which the essential feature is the identification of labelled anatomical structures. The book can be recommended as an introductory learning tool for those starting to study CT scans of the body including candidates for Part 1 – F.R.C.R.

I. Kelsey Fry.

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Real-time ultrasound. A new method for studying gall-bladder kinetics

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ABSTRACT

Real-time ultrasound has been found to be a satisfactory method for studying changes in gall-bladder size. It is superior to many other methods since it is non-invasive, harmless, and does not rely on the metabolism of a contrast agent. We have also found it easy to identify and compensate for changes in the gall-bladder axis. Rapid serial images are easily obtained and show similar contraction patterns to those resulting from conventional techniques.

Today gall-bladder disease is the commonest indication for major abdominal surgery in this country and gall-stones are responsible for 1% of all deaths. The frequency and efficiency of gall-bladder emptying are probably important factors influencing crystallization and stone formation (Bouchier, 1977).

Serial radiography is an important method of studying gall-bladder contraction (Boyden, 1928; Edholm, 1960; Park, *et al.*, 1970). However, this technique relies on the normal metabolism of a contrast medium and may suffer errors due to magnification which are increased by gall-bladder movements. There is a significant radiation exposure and the observations are intermittent. Radioisotopic techniques (Englert and Chiu, 1966; Chapple *et al.*, 1975) permit continuous recordings but otherwise have the same problems as radiography. Indwelling tubes placed at surgery and timed aspiration of bile from the duodenum are unphysiological and imprecise.

Grey scale B-scan ultrasonography can visualize the gall-bladder outline in 95% of fasting patients with a diagnostic accuracy of 90–98% (Gonzalez and Johnson, 1978). Real-time ultrasound has a comparable accuracy (Lutz, *et al.*, 1976). This investigation plans to demonstrate that real-time ultrasound, because of its relative ease of use and high success rate, and because it is harmless and does not depend on contrast media, is a suitable method for studying gall-bladder size, mobility and response to cholecystokinetic stimulation.

METHOD AND MATERIALS

Fourteen male volunteers aged between 23 and 41 years were examined. They had no history or symptoms of gall-bladder disease and were taking no medication. They were fasting for a minimum of eight hours but received no other preparations. A Diasonograph (Nuclear Enterprises 4200) with a mechanically operated real-time probe (NE 4260) was used to scan the right subcostal region of the subjects. The attenuation and time-gain compensation were adjusted and the probe rotated about its long axis and its angle of elevation altered until the maximum area of gall-bladder neck, fundus and body was viewed on the screen. When correct positioning of the probe was obtained a single frame of the real-time image was stored on the scan convertor. Data could be added to this image by a character generator. Copies of the still image were obtained using a Tektronix Video Hard Copier, and photographs taken using a Vidicam Unit. Scanning normally took place with the subject supine and with breath held in inspiration. In three cases it was found necessary to have the subject erect.

After obtaining several hard copies of the fasting gall-bladder, each subject was given an oral cholecystokinetic agent. In all cases this was Biloptin fatty meal (Scheering, Berlin) mixed in a cup of water. This took 10 to 15 seconds to swallow and timing began as the cup was emptied.

The first two subjects were scanned at five minute intervals to check the technique and discover and erradicate any major problems. After this, subjects were scanned at two-minute intervals for 40 minutes. For each subject a series of video hard copies was obtained from which the area of the gall-bladder was measured using planimetry. The areas were expressed as a percentage of the original fasting area.

RESULTS

The gall-baldder was completely visualized in 13 cases. One was not viewed because of its position behind bowel gas. The initial area of the gall-bladder varied from 7.3 to 15.9 cm^2. In 12 cases there was a reduction in area of about 50% by 30 to 40 minutes; this represents a reduction in volume of about 70%. In one case (13) there was only a 7.5% fall in area over

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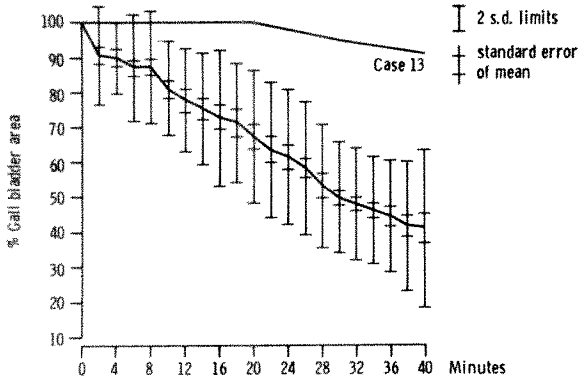

Fig. 1.

The mean, standard error of the mean and two standard deviation limits for measurements taken at two minute intervals from ten normal gall-bladders after administration of a fatty meal. The change in the slope of the mean at eight minutes is statistically significant.

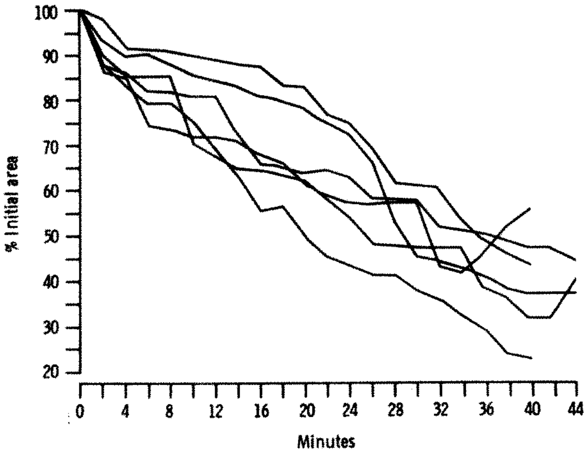

Fig. 2.

The patterns of contraction of six gall-bladders in which the intitial rapid emptying, and subsequent short pause were well seen.

this time (Fig. 1). This gall-bladder had a small calculus lying on the anterior wall and the neck was filled with biliary sludge. Excluding this abnormal gall-bladder and the two preliminary scans, the mean and normal distribution were calculated for all the measurements at two minute intervals and the results expressed graphically (Fig. 1).

Three of the gall-bladders showed folding of the body back onto itself, and these may be examples of the Phrygian cap. All three examples showed good gall-bladder contraction. In most subjects it was noticed that the gall-bladder was not static during contraction and in some cases its long axis swung laterally 45 deg or more. It was noticed that when the gall-bladder became very small the partial volume effect resulted in its filling with echoes from surrounding structures, and visualization then became impracticable.

Discussion

Of the 14 gall-bladders 13 were visualized, a success rate of 93% which compares favourably with published results of 95% (Gonzalez and Johnson, 1978). One gall-bladder was shown to be abnormal as its area only contracted by 7.5% compared to at least 50% in the ten gall-bladders which were observed at two minute intervals.

Six of these gall-bladders showed a contraction pattern which followed closely the pattern of the mean line of the normal distribution graph. There was a period of rapid emptying followed by a pause lasting two or more minutes. This was followed by a period of almost linear fall in area and then frequently by rather erratic contraction (Fig. 2). This pattern has been described in previous work and the pause termed "the two minute pause" by Boyden (Boyden, 1928; Edholm, 1960; Englert and Chiu, 1966). The fact that our real-time ultrasound study also demonstrated this phenomenon indicates that the technique accurately monitors gall-bladder function. Two gall-bladders showed a static period of several minutes before emptying progressively without a subsequent pause. The remaining two gall-bladders showed great variation in size over the first ten minutes, sometimes increasing and decreasing alternately. It is likely that in these cases the maximum gall-bladder area was not seen at every observation.

There was evidence that two gall-bladders had started to refill before observations ended, yet in another four cases the gall-bladders were still contracting vigorously. Several problems were encountered including non-visualization due to bowel gas casting ultrasonic shadows, and poor visualization when the size of the object nears the width of the ultrasound beam (3 mm) and echoes produced by surrounding structures impair the image. The method also depends on operator expertise and the subjective element this involves.

In spite of these problems, real-time ultrasonography is a relatively easy technique and requires no contrast medium, does not depend on gall-bladder function and is apparently harmless. Images are repeatable at any suitable interval and there is no unknown magnification factor. Changes in gall-bladder axis are readily seen and easily corrected. We believe that this technique is suitable for use in the clinical assessment of gall-bladder function as well as in a research role for studying the causes and effects of gall-bladder disease.

Real-time ultrasound. A new method for studying gall-bladder kinetics

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Book reviews

Asbestos-related Disease. By Leslie Preger with D. T. Arai, P. Kotin, H. Weil and J. Werchick, pp. ix+261+index, illus. 1978 (Grune and Stratton, Inc. New York, U.S.A.) £15·90.
ISBN 0-8089-1083-3

The publication of this comprehensive book comes at an opportune time. Many of those whose exposure to asbestos during the last war and subsequently has led to asbestos-related disease are reaching a stage in this chronic condition where incapacity and the potential for malignant change is approaching a peak. These patients are nearing retirement, when they may move to a part of the country less familiar with the changes to be expected. The main author is a radiologist, and it has been written and illustrated largely as an approach to the radiological problem.

The opening chapter by two of the co-authors is a succinct and well written description of the clinical findings, with wise counsel on the management of the patient. The two closing chapters on the industrial medical officer's resposibility and medico-legal aspects, while dealing with the situation obtaining in America, also provide good advice for the radiologist. The rest of the book describes the pathological findings and their radiological manifestations.

Computer retrieval has gathered many of the important papers on this subject from the world's literature. There are 328 references, the majority from non-radiological journals, which form the basis of the pathological and radiological description. The lesions are difficult to reproduce photographically, but the author has succeeded with his own material and with the courtesy of other authors in gathering a wide selection of examples of radiographs, including CT scans, radioisotope scans and tomograms. The quality of the photographic reproductions is good and representative of the pathology.

This book of 260 pages is elegantly produced, of a comfortable size to read in a chair or on a journey, and contains in a thoroughly readable form a digest of the current knowledge of asbestos disease.

F. A. F. MACKENZIE.

Neurology. By Edwin R. Bickerstaff and P. H. Schuur. pp. 204, illus. 3rd ed., 1978. (Hodder and Stoughton, Sevenoaks, Kent) £2·45 paperback/£4·95 hardback.
ISBN 0-340-23166-1

Written for the junior doctor and those in the nursing and ancillary professions, the bulk of this inexpensive book deals in the main with neurological diseases. There are also two excellent chapters by Mr. Peter Schuur on neurosurgical operations and procedures, and others on basic aspects of the nervous system, neurological investigations, aspects of neurological nursing, and an interesting chapter on the nurse's special responsibility in neurology. There is a glossary of neurological terms and an appendix of selected normal values, and whilst there is a good index, references to larger texts are not included.

There are, however, a number of areas which require criticism. For example, neurological complications of imbibing bush tea, references to the bygone hat-making industry, and syphilis as a cause of Parkinson's disease appear out of place in this sort of book, and give an impression of older texts and earlier days. Whilst poliomyelitis is considered at length, pyogenic meningitis receives only scant attention, and tetanus none at all. There is no mention of risks or precautions to be taken in the "Tensilon test", and the section on post-herpetic neuralgia (page 133) is both ill-conceived and inaccurate. There are also spelling errors—inexcusable in this third edition. Thus, phenytoin, caeruloplasmin, Megimide (trade name), Klippel-Feil and Jakob-Creutzfeldt are all mis-spelt in places. There is also unnecessary inconsistency in drug nomenclature, with a number of drugs appearing haphazardly, sometimes as trade names and sometimes as their proper names.

In summary, this is a good book in concept. Despite being the third edition and some up-to-date information, for instance computerized tomography, being included, future editions require considerably better editing, up-dating and correction.

G. D. SCHOTT.

1979, *British Journal of Radiology*, *52*, 804–809

The dose to the patient and the quality of the image in xeromammography

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(*Received December 1978 and in revised form May 1979*)

ABSTRACT

Radiation dose levels in xeromammography were measured both on entry and exit surfaces of the breast. The mean skin dose in the upper inner quadrant was 2.4 rad for a complete examination. The addition of 1 mm aluminium filtration reduced this dose to 1.6 rad. The mean dose to the breast tissues is, however, a more meaningful indication of potential hazard from mammographic investigations and entrance and exit dose measurements enable this to be assessed.

The ability of xeroradiography to image small glass beads was assessed by visual detection tests on specially prepared phantoms and compared with earlier work on conventional mammography using industrial film and film–screen systems. With only inherent tube filtration the performance of xeroradiography was comparable to that of industrial film. The addition of 1 mm aluminium filtration as a means of reducing the dose received by the patient reduced the performance of xeroradiography to approximately that of a medium-speed mammographic film–screen system. The incorporation of tissue-equivalent scattering material further reduced the detection capability of xeroradiography as it does also for film–screen systems.

In an earlier paper (Asbury and Barker, 1975), dose levels to the skin of the breast resulting from mammography were measured for techniques using industrial film and for those using various film–screen combinations. Subsequently, we reported the use of visual detection tests to assess the imaging capabilities of these same systems (Moores *et al.*, 1979). Receiver operating characteristic curves (ROC) were constructed to determine the ability of each system to image small glass beads. This was done both with and without the addition of breast-equivalent scattering material.

This work has now been extended to xeromammography. Our aims were: (1) to measure the dose received by the patient in xeromammography; (2) to assess the ability of xeromammography to image small glass particles, again employing signal detection theory; (3) to determine the effects of scattering material; (4) to measure the effects of additional beam filtration on both the dose to the patient and the detectability of small particles; and (5) to compare these results with those of our previous work with industrial film and film–screen combinations.

MATERIALS AND METHODS

Measurements of dose

The radiation dose to the skin of the upper inner quadrant of the breast was measured using lithium fluoride thermoluminescent dosimetry, as previously described (Asbury and Barker, 1975). Each examination consisted of cranio-caudal and medio-lateral views. Compression was applied in both projections using a soft balloon inserted into the end of the collimating cone. At the same time, the dose on the exit surface of the breast was measured by placing a lithium fluoride sachet under the centre of the breast. These measurements were performed firstly on 25 patients with only the inherent tube filtration (equivalent to 0.7 mm Al) and secondly on another 25 patients with the addition of 1 mm Al filtration.

Design of phantom

In our earlier work on visual detection, Perspex phantoms measuring 10 cm × 10 cm × 0.5 cm were divided by fine wire into 100 squares of equal area. Unfortunately, these phantoms could not be used with the Xerox system because the intense edge enhancement produced by the dense wire caused a deficiency of powder within the 1 cm × 1 cm sample areas. A similar undesirable enhancement effect occurred at the edges of the phantom, affecting the outermost row of squares. To overcome these problems, larger Perspex phantoms measuring 12 cm × 12 cm × 0.5 cm were constructed and 0.5 mm deep grooves were made at 1 cm intervals to separate the individual sample areas. Only the 100 innermost squares were used so that both problems associated with edge enhancement were overcome.

As in the previous investigation (Moores *et al.*, 1979), soda glass beads were sorted into six different size groupings, as detailed in Table I. Particles of a given size were randomly distributed among 50 of the 100 sample squares and were secured by adhesive

TABLE I

THE MEAN DIAMETERS OF THE BEADS EMPLOYED IN EACH OF THE SIX TEST PHANTOMS

Mean bead diameter, μm	160	198	254	299	356	400
Standard deviation, μm	4	8	8	10	8	7

tape. No sample square contained more than one bead. Six phantoms, each with a different particle size, were constructed in this way.

Radiographic conditions

The X-ray tube used was a Dynamax HD50D with a rotating tungsten target and focal spot sizes of 2 mm and 1mm. The smaller focal spot was used throughout for all of the images of the phantoms. Typical exposure factors used during the clinical dose measurements were FFD 85 cm, kV 37–45, mAs 100–160 with no additional filtration, and mAs 120–180 with 1.7 mm Al total filtration. The kV was measured using an Ardran-Crooks penetrameter which had been calibrated at the National Physical Laboratory. The phantoms were imaged using a measured kV of 41 and an FFD of 85 cm. The manner of determining correct exposure for the phantoms is described later.

Phantoms were imaged both with and without 4 cm of tissue-equivalent scattering material (White, 1977), both with and without additional beam filtration. The extra 4 cm of material was placed immediately above the phantom. The xeroradiography equipment consisted of the standard Xerox system 125. The density and contrast settings C were used throughout and all images were produced in the positive mode.

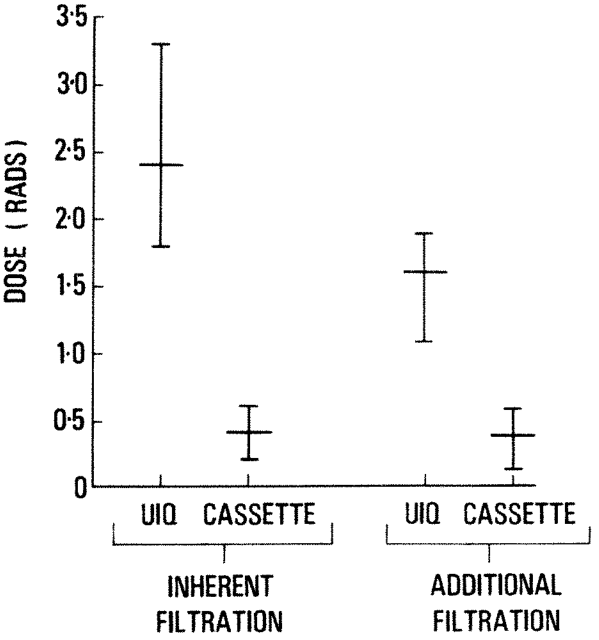

Fig. 1.

Total skin dose to upper inner quadrant (UIQ) and exit dose for xeromammography.

Data analysis

All of the Xerox images were viewed using reflected light from a standard X-ray illuminator. The 24 test images were reported on by three observers and the data so obtained were averaged and analysed as in our previous communication (Moores *et al.*, 1979).

Results

Measurements of dose

These are illustrated in Fig. 1. The mean total dose to the skin of the upper inner quadrant of the breast in the group of 25 women imaged with only the inherent tube filtration of 0.7 mm Al equivalent was 2.4 rad (range 1.8–3.3 rad). The mean exit dose was 410 mrad (range 220 mrad–610 mrad). When 1 mm of Al filtration was added these doses fell to 1.6 rad (range 1.1–1.9 rad) and 380 mrad (range 130–580 mrad). The added filtration produced an average reduction in entrance dose of 33% while the exit dose was reduced by only 7%.

Radiographs of phantoms in scatter-free conditions

Figure 2 shows the average ROC curves derived from xeroradiograms of the six phantoms in scatter-free conditions both with and without additional filtration. Phantoms with particle diameters greater than 198 μm gave 100% true positive detection for all false positive probabilities and these results have not, therefore, been included.

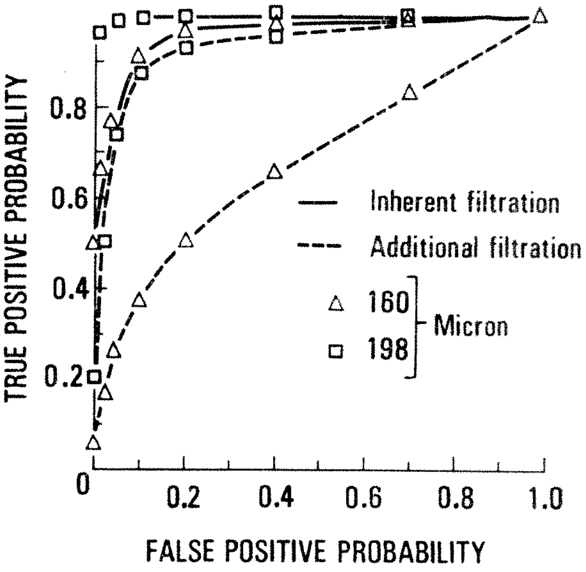

Fig. 2.

Averaged receiver-operating characteristic (ROC) curves for different particle sizes imaged without scattering material on the Xerox 125 system, with and without 1 mm Al additional filtration.

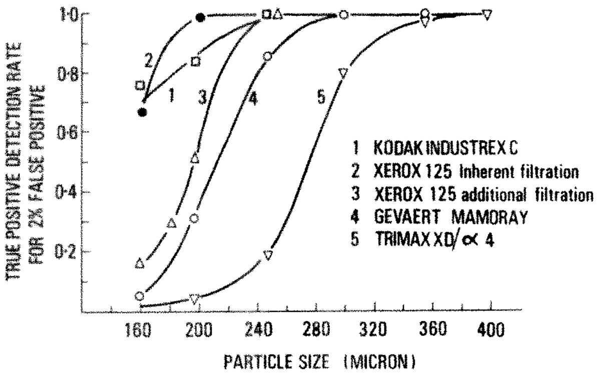

Fig. 3.

True positive detection rates, at the 2% false positive level, for different particle sizes imaged without scattering material.

For a given particle size and false positive detection rate, the true positive detection rate was consistently reduced when additional filtration was used. In order to make these ROC results more easily understood, the procedure adopted in the previous investigations was employed. The true positive detection rate corresponding to a 2% false positive level was extracted from each ROC curve. Figure 3 shows the results for the different particle sizes without the addition of scattering material. The results obtained for xeroradiography are shown together with those for both a fast (Trimax XD–α4) and a medium speed (Agfa-Gevaert Mamoray RP3–MR50) film-screen system, and also for a slow (Kodak Industrex C) film system previously investigated. The performance of xeroradiography with only inherent filtration present was comparable with that of the industrial film. When a 1 mm Al filter was added to the beam the true positive detection rate deteriorated so that the particle size for 50% true positive detectability increased from 150 μm (by extra-polation of curve 2) to 200 μm and was then comparable with the performance of the medium-speed film–screen system.

Radiographs of phantoms with addition of scattering material

The result of adding scattering material is demonstrated in Fig. 4. There was a decrease in the performance of xeroradiography which can be observed by comparing curve 2, Fig. 4 with curve 2, Fig. 3. With inherent tube filtration alone the addition of scattering material reduced the detection capability of xeroradiography so that the particle size for 50% true positive detection increased from 150μm to 260 μm. An effect of similar magnitude was observed when the beam had first been hardened using an additional 1 mm Al filtration (curve 3 Figs. 3 and 4).

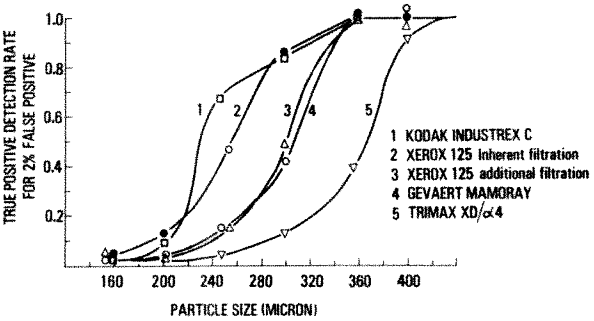

Fig. 4.

True positive detection rates, at the 2% false positive level, for different particle sizes imaged with scattering material.

As in the previous investigation (Moores *et al.*, 1979), the areas under the detection curves and the particle sizes for 50% true positive detection were used as indices of performance and are given in Table II for xeroradiography. Also shown are the previously published results for industrial film and for two of the film–screen combinations. Xeromammography with no added filtration is comparable in performance to industrial film. With added filtration its performance approximates more to that of a medium-speed film–screen system (Agfa-Gevaert Mamoray).

Discussion

In mammographic screening surveys of well-women it is recommended that the dose received by the patient for an annual examination should be less than 2 rad (Ellis, 1972). With inherent filtration alone (0.7 mm Al equivalent) the mean total skin dose of 2.4 rad is 20% higher than this suggested level. We have shown that the dose received by the patient in xeromammography can be decreased to a level suitable for screening by the use of 1 mm Al additional filtration. This reduced the mean skin dose per examination to 1.6 rad.

Skin dose may provide a suitable assessment of potential hazard from mammographic investigations which employ similar X-ray beam qualities. However, the induction of breast cancer is more likely to be related to the average dose received by the breast than to the skin dose and this distinction is shown to be of practical importance when comparing conventional film imaging with xeroradiography. The mean dose to the breast is given approximately by:

$$D_{\text{mean}} = \frac{(D_{\text{en}} - D_{\text{ex}})}{\ln (D_{\text{en}}/D_{\text{ex}})}$$

where D_{en} is the entrance dose and D_{ex} is the exit

TABLE II

Performance indices of the film–screen combinations and the Xerox 125 system with scattering material

Imaging system	Measured kV	Total filtration, mm Al	Particle size for 50% detectability, μm	Area under detectability curve
3M Trimax XD–Film 3M Trimax α4 Screen	30	0.5	368	42.7
Agfa-Gevaert RP3 Film Agfa-Gevaert MR50 Screen	30	0.5	308	69.3
Kodak Industrex C Film	30	0.5	230	97.3
Xerox 125 system	41	1.7	301	75.5
Xerox 125 system	41	0.7	257	94.4

dose (Andersson *et al.*, 1977). In the present investigation the entrance and exit doses in xeroradiography were measured both with and without additional tube filtration. In film mammography with a molybdenum anode tube the exit dose from an average breast is taken to be 3% of the entrance dose (Boag *et al.*, 1976).

Table III gives the results of the clinical measurements and illustrates the following points:

(1) The skin dose and mean dose to the breast tissues are directly related when similar X-ray beam qualities are employed. The ratio of skin dose to mean dose is 3.6 and is constant to within 1% for the molybdenum target. Therefore, both the mean dose and skin dose vary by a factor of 27 for the film systems used.

(2) There is no simple relationship between skin dose and mean dose to the breast tissues when different X-ray beam qualities are used. The ratio of skin dose to mean dose is 1.88 for the tungsten target with total filtration 1.7 mm Al equivalent and 2.12 for the tungsten target with only 0.7 mm filtration. Both are very different from the value with the molybdenum target. Consequently, although the skin dose for the Agfa-Gevaert film system with molybdenum target was 75% of the value for the Xerox system with 1.7 mm Al filtration and tungsten target, the mean breast dose for the Agfa-Gevaert system was only 38% of the value for the Xerox system.

These variations arise from the different kV and target material used in the two techniques and from the further beam hardening effect of additional filtration. Meaningful discussion of the possible risks of induction of breast cancer by different mammographic techniques is unlikely until agreement can be reached on the most suitable method of presenting the data. We suggest that doses should always be quoted in terms of mean dose to the breast tissues.

Before considering the effect of dose reduction on image quality in xeroradiography some explanation must be given of the method used to obtain correct exposures of the test phantoms.

Correct exposure for film systems normally occurs when the density lies on the linear portion of the characteristic curve. A film density of unity usually satisfies this condition. On the other hand, the characteristic curve of the Xerox system is not as important in the imaging process (Evans *et al.*, 1975). It has been shown that at the optimum exposure in xeroradiography the energy deposited in the selenium plate is roughly constant for different X-ray beam qualities and that this exposure can be determined objectively by maximizing the width of the enhancement of a low-contrast edge (Jaeger *et al.*, 1978). In the present work the effects of exposure on particle detectability were quantified using ROC analysis. Figure 5 shows a typical variation in the position of the average ROC curve when a given phantom was subjected to different exposures. For a 27% change in exposure the true positive detection rate for 2% false positive detection can drop by as much as 40%. It is often implied that one of the advantages of xeroradiography is its wide exposure latitude. This study confirms the clinical impression that, certainly at the exposure levels used in mammography, an optimum exposure is vital for appreciation of fine detail. Optimum exposure occurs when the true positive detection rate is maximized, and in the present investigation the optimum exposure was determined in this way and used for each of the xeroradiographic regimes.

An evaluation of the statistical validity of the techniques used in the analysis was presented in our previous paper (Moores *et al.*, 1979) and the interested reader is referred to that discussion.

Consideration is now given to the relationship between dose reduction by the addition of beam filtration and image quality in xeroradiography. Examination of Table II shows that with inherent filtration alone xeroradiography has a particle-imaging capability only slightly worse than that of the industrial film. When a 1 mm Al filter was added to the beam the performance was comparable with that of the medium-speed film–screen combination. It was noted in the earlier paper on industrial film and film–screen combinations that when a faster system was used there was an accompanying decrease in detectability of small particles. Xeroradiography shows the same general trend but the reasons for this are not the same.

The reduction in skin dose to the patient when additional filtration was used in xeroradiography results mainly from the production of a harder X-ray beam. The decrease in particle detectability may be due to the reduction in contrast which accompanies this beam hardening. With film–screen systems on the other hand, reduction in dose results from a reduction in the number of X-ray photons used to form the image, so that a large contribution to the observed decrease in small particle detectability is due to the increased noise.

The results presented in Figs. 3 and 4 clearly show that xeroradiography, like film mammography, is significantly affected by scattering material at least as far as detectability of small particles is concerned. Although the presence of tissue-equivalent material increases the scattered radiation incident upon the cassette it can also be considered as an additional filter which has a beam hardening effect (Fitzgerald *et al.*, 1979). Both degrade the image by reducing the X-ray contrast at the cassette. However, scattered radiation will have a significant effect in mammography since it has been shown that in a typical examination the ratio of scattered to primary radiation can be as high as 0.55 (Barnes and Brezovich, 1978). In film mammography, conventional means of reducing scattered radiation such as grids or air gaps are not feasible. In electrostatic imaging, however, the use of an electrostatic grid in the

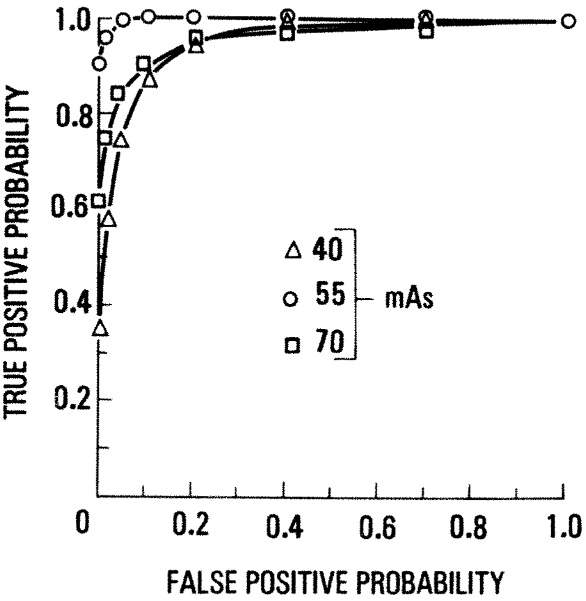

FIG. 5.

Averaged ROC curves for different exposures of the 254 μm phantom imaged on the Xerox 125 system with 1 mm Al additional filtration and without scattering material.

TABLE III

CLINICAL DOSE RESULTS FOR FILM–SCREEN COMBINATIONS AND XEROX 125 SYSTEM

Imaging system	Anode material	Mean skin dose (upper inner quadrant) total examination, rad	Average dose to breast, rad
3M Trimax XD–film 3M Trimax α4 screen	Molybdenum	0.18	0.05
Agfa-Gevaert RP3 film Agfa-Gevaert MR50 screen	Molybdenum	1.2	0.33
Kodak Industrex C film	Molybdenum	4.9	1.36
Xerox 125 system 1.7 mm Al total filtration	Tungsten	1.6	0.85
Xerox 125 system 0.7 mm Al total filtration	Tungsten	2.4	1.13

development process has been successfully applied (Muntz *et al.*, 1976), and there may, therefore, be potential for further improvement of the Xerox image.

Even without such further developments, xeromammography with added beam filtration is a suitable alternative imaging system for breast cancer screening programmes in terms of both its dose levels and its imaging capabilities. However, the addition of aluminium filtration in order to reduce the dose to the patient produces a corresponding reduction in detectability of small particles. The level of detectability which results is, in fact, similar to that observed with film/screen combinations which involve similar dose levels to the patient.

Acknowledgments

We wish to thank the North Western Regional Health Authority for providing funds for this work.

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White, D. R., 1977. The formulation of tissue substitute materials using basic interaction data. *Physics in Medicine and Biology*, *22*, 889–899.

Book reviews

Préparation Des Sources Radioactives Pour Mesures D'Activité. By Yves le Gallic, pp. 53, 1978 (Commissariat à L'Energie Atomique, France) Fr. 50.00.
ISBN 0150-231-X.

This monograph is a review of source preparation techniques used in radioactivity measurements and contains experimental details of procedures in use in many national and international standardizing laboratories.

The accurate dilution of radioactive solutions and preparation of aliquots are described at length, special consideration being given to the performance of microbalances and the use of micropipettes and microburettes in these operations. The preparation of thin metallized plastic films for source mounts together with apparatus for measuring their thickness and electrical conductivity are then described. Typical carrier concentrations and acid strengths necessary to obviate absorption phenomena in containers of radioactive solutions are listed for a large number of elements, and methods for the preparation of thin, high efficiency sources are outlined. Quantitative effects of backscattering, self absorption and source absorption are given for α and β particles over a wide range of energy.

The text is logically presented with good indexing to specific topics, figures and tables. Although some of the axes of graphs could be more explicitly labelled, the tables, figures, photographs and mathematical formulae are in general easy to interpret.

This monograph adequately supplements other more specialized reviews on a similar subject matter, and while it will be of obvious value to radionuclide metrologists it may have only limited interest for radiologists in general.

I. W. Goodier.

The Pathogenesis of Colorectal Cancer. By B. C. Morson, pp. xi + 164, illus., 1978 (W. B. Saunders Co., Philadelphia, London, Toronto) £17·50.
ISBN 0-7216-6558-6

The tenth volume of the series Major Problems in Pathology is devoted to colorectal cancer. A distinguished Anglo-American team of pathologists and clinicians has contributed to this volume and the team is directed by Dr. Basil Morson from St. Mark's Hospital, London. The volume consists of approximately 160 pages divided into 12 chapters each of which has a separate bibliography and which are well illustrated. The introductory chapter is an overall view of the incidence and aetiological factors known to be associated with cancer of the large gut and is written by Dr. Morson. There follows a description of the various types of polyp, both benign and malignant, that occur in the large bowel and there is also a separate chapter devoted to the multiple polyp syndromes. A great deal of attention is focused on the known pre-malignant conditions, namely adenoma, polyposis coli and ulcerative colitis. The relationship between ulcerative colitis, epithelial dysplasia and carcinoma is also well covered. Two chapters on the epidemiology of polyps and cancer complete this volume and they discuss the variable incidence of cancer of the colon throughout the world, the possible reasons for this and the interrelationships of genetic and environmental factors in its cause. This is an excellent book of manageable size which should be read by all those who deal with the clinical and pathological problems of large bowel disease.

A. Read.

1979, *British Journal of Radiology*, 52, 810–815

The influence of location of the crossing needle on dose distributions from planar implants

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(Received May 1978 and in revised form September 1978)

Abstract

Three typical planar radium implants with one uncrossed end were investigated for optimization of the crossing needle location. Isodose distributions in a plane 0.5 cm from the plane of the implant were calculated and the sizes and shapes of the areas receiving at least 85% of the maximum dose were evaluated. The merits of each implant geometry are discussed along with certain clinical considerations. As a refinement to the Paterson-Parker rules of geometry, it was found that an optimum distribution is achieved when the crossing needle is located near the physical ends of the parallel needles.

The Paterson-Parker system, developed in the mid-1930's, gave radiotherapists a modern convention of dosage distribution when certain geometrical rules were used in planning radium moulds and implants (Paterson and Parker, 1938). By following the classical distribution rules, an optimal dose can be delivered within the treatment volume, with a variation of 10 to 12% of the mean calculated dose being encountered in occasional small areas. Unfortunately, tumours in human tissue often do not lend themselves to placement of a perfectly geometrical implant and this results in areas of under- or over- dosage within the treatment volume. Placement of the crossing needle is one such aspect of the implant technique that may be affected by tumour geometry and the radiotherapist's surgical abilities. The relationship between the site of the crossing needle and the optimal dose-volume will be demonstrated to be of significance in planning a radium implant.

It is generally accepted that the crossing needles of an interstitial implant should not be more than 1 cm away from the active ends of the needles. This is specified in the geometry originally described by Paterson and Parker (1938) which, if followed, would yield a reasonably uniform distribution of dose in a volume surrounding a planar implant. In this dosimetry system, provisions were made for implants with only one crossed end. This, of course, is an important consideration since many planar implants are used in areas where it becomes difficult to cross both ends yet still maintain an implant with geometry as specified in the distribution rules.

The purpose of this report is to show that while the original distribution rules remain the accepted method, in view of their geometrical elegance and computational simplicity, there is also a narrow range for the location of the crossing needle whereby the dose distribution can be optimized. This range, in most cases, is within 2 mm of the physical ends of the parallel radium needles (as opposed to the original 1 cm range). It is interesting to note that, in most instances, the crossing needles will cross as close as possible to the ends of the physical lengths. This can be illustrated when viewing the isodose distribution of various implant sizes and geometries. Three different implants with standard Paterson-Parker geometries were investigated for optimization of the location of the crossing needle. They range in size from approximately 17 cm^2 to 34 cm^2.

Method

Isodose distributions were obtained with an Artronix PC-12 computer. The method used by the computer is, essentially, a Batho-Young table linear generator program which is determined by evaluation of Sievert intervals (Young and Batho, 1964; Sievert, 1930). Solutions may be obtained in terms of dose in rads by specifying an exposure-rate constant and a roentgen-to-rad conversion factor. While the literature reveals a small degree of uncertainty about the Paterson-Parker roentgen-to-rad conversion (Porter, 1970), this is not a factor in our results because all isodose curves are expressed in relative percentages. An effective absorption coefficient for the platinum filtration is also specified.

A routine is employed in the program to account for oblique filtration. Self-absorption of the source, which may have a considerable effect on the dose near the ends of the needles, is not allowed for. This, however, is not expected to be of importance in the overall dose distributions.

Results

All three geometries investigated were of the Paterson-Parker type. The first geometry shown, however, will be referred to as a standard Manchester implant (Fig. 1) since it consists of six parallel needles spaced 0.8 cm apart with two crossing needles at one end. The four inside parallel needles contain 1.0 mg radium and the two outside parallel needles 2 mg radium. The two crossing needles each contain 1.33 mg radium. Figure 2 illustrates an implant with parallel needles of the same type as the Manchester implant, but the spacing is 1 cm apart. This will be referred to as the small Paterson-Parker implant. The crossing needle contains 2 mg radium. The largest implant, illustrated in Fig. 3, consists of parallel needles of 3 mg radium on the outside and four 1.5 mg radium needles on the inside which are spaced 1 cm apart. The crossing needle contains 3 mg radium.

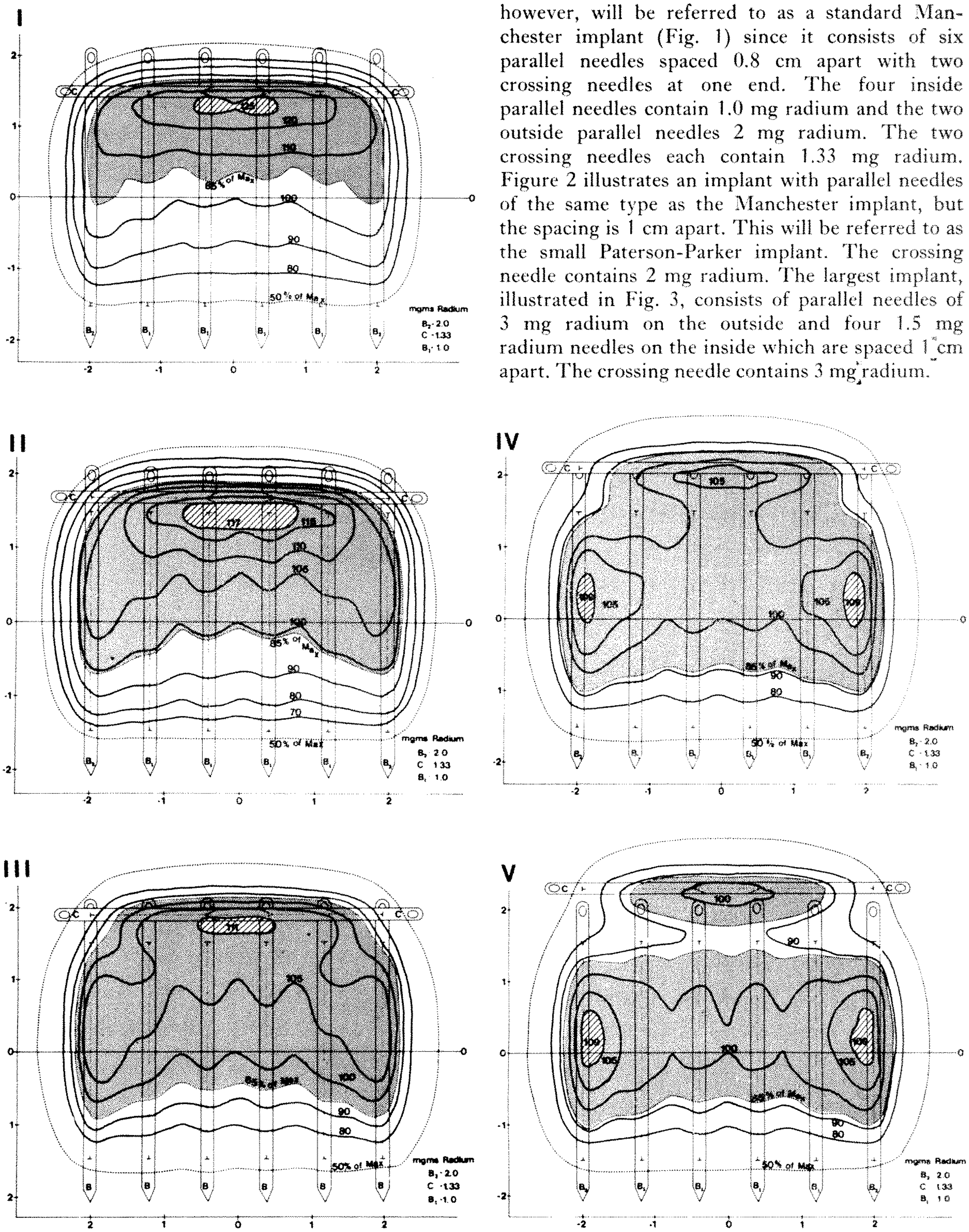
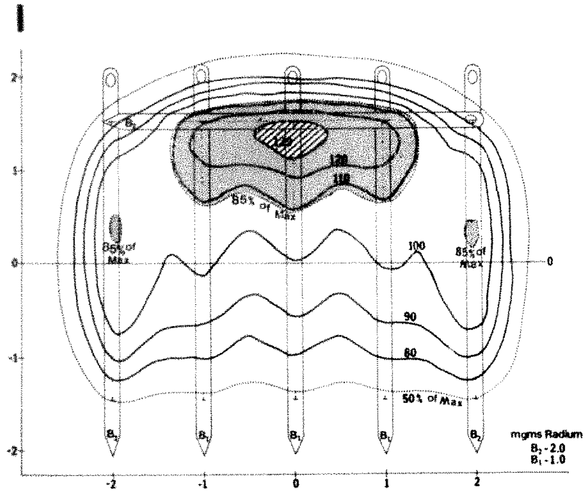


Fig. 1.
Manchester implant.



With the exception of the location of one crossing needle in the large implant, the crossing needles are located at 0, 2, 4, 6, and 8 mm from the end of the active lengths of the parallel needles. In the two smaller implants, the distance from the active end to the physical end is 6 mm. In the large implant, a distribution is shown for the crossing needle at 6.5 mm since this is the distance from the active to the physical end of the 1.5 mg and 3.0 mg needles.

Isodose curves (calculated in a plane 0.5 cm from the needles) for all three implants are shown for five different locations of the crossing needle. The curves are normalized to the dose occurring at the geometrical centre of the parallel needles. The shaded region is the area which receives at least 85% of the maximum dose.

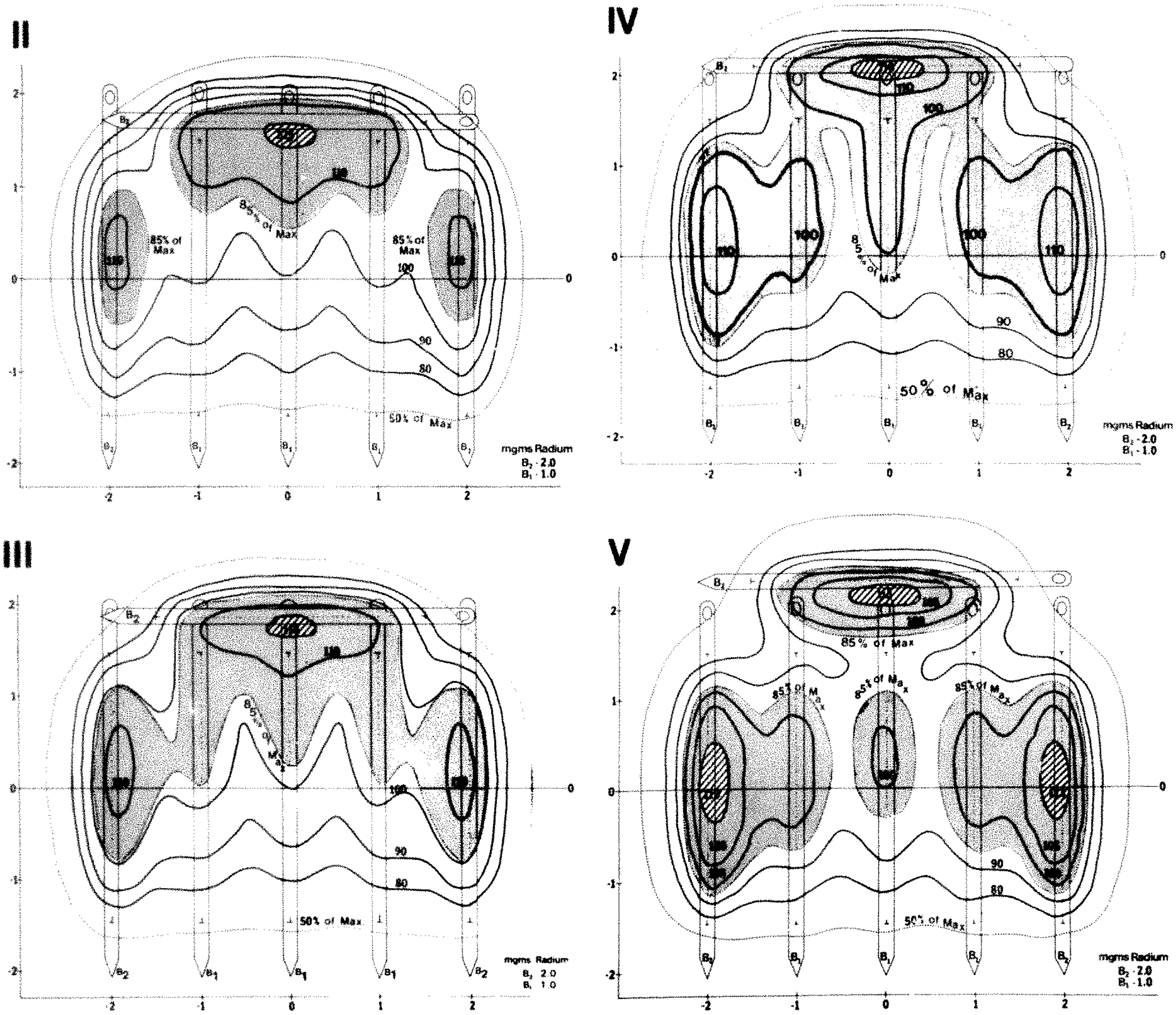
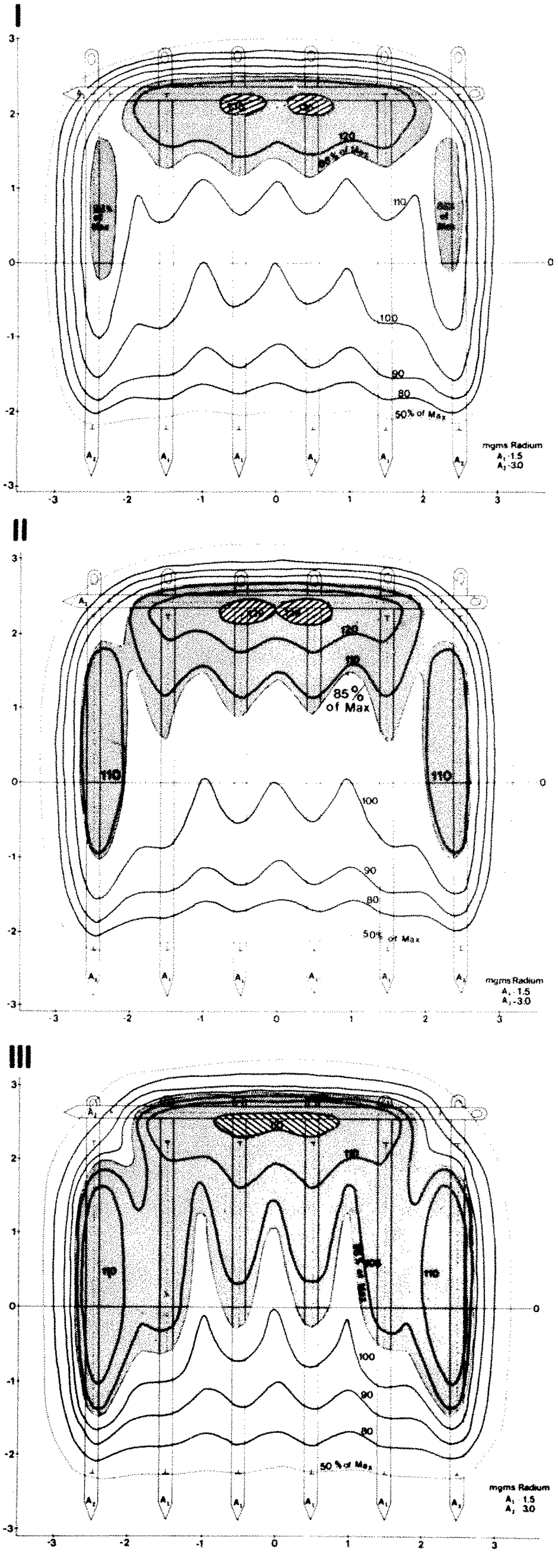


FIG. 2.
Small Paterson-Parker implant.

The area that receives 85% or more of the maximum dose (hereafter called the 85% area) is plotted against the distance of the crossing needle beyond the active ends of the parallel needles in Fig. 4. One should note that all three implants, which are of varying sizes, are plotted on the same scale. The arrows indicate the size of the 85% areas which result when the crossing needles are at the physical ends of the implant.

While this plot is meaningful because it indicates the 85% area to be at a maximum when the crossing needle is at or very near the physical ends, it cannot be very helpful in comparing the three different implant geometries. A larger implant, of the Paterson-Parker type, would be expected to yield a larger 85% area. However, the important



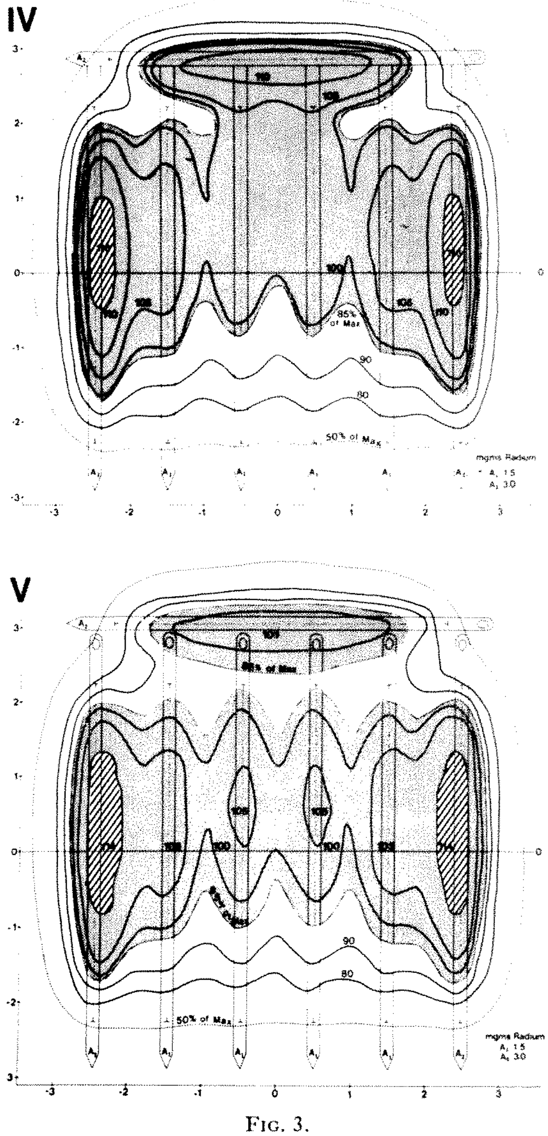


FIG. 3.
Large Paterson-Parker implant.

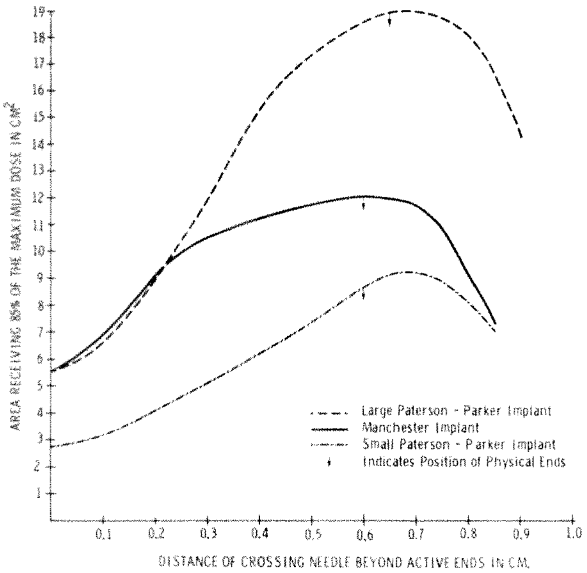


Fig. 4.

Area receiving 85% of the maximum dose in cm².

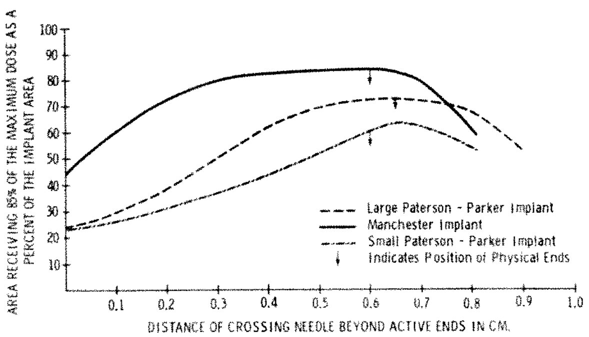


Fig. 5.

Area receiving 85% of the maximum dose as a percent of the implant area.

consideration is how well the 85% area covers the physical area of the implant. This illustration of geometrical efficiency would be a useful indicator of an index of uniformity. An index of uniformity (in the form of a graph) allows the radiotherapist to compare the geometrical efficiency of different implants by normalizing the 85% area to the actual implant area.

As a method of normalization for implants of different geometries, a graph showing the 85% area as a percentage of the implant area is plotted against the distance of the crossing needle beyond the active ends in Fig. 5. This type of plot can serve as an index of uniformity which would be useful in comparing the merits of any implant.

Discussion

Practical geometries which yield a high uniformity index are clinically important, preventing over-irradiation or dosage inhomogeneities. Over-irradiation can lead to either necrosis or fibrosis or both, while under-irradiation can result in tumour recurrence (Fletcher and Stovall, 1962). Radiotherapists have always given priority to anatomical coverage of the lesion rather than rigid adherence to geometrical implant patterns, even though unusual implant patterns may place the patient at risk for necrosis.

When Fletcher and Stovall (1962) examined the causes of necrosis and recurrence in 157 patients with oral cavity tumours who were treated at M. D. Anderson Hospital and Tumor Institute from 1948 to 1959, two recurrences were found in the T1 group and six in the T2 group.* Seven of the recurrences could be attributed to either inadequate anatomical coverage of the lesion, or to adequate coverage but with a low dosage.

Eleven instances of necrosis were seen in the same study, five of which occurred in regions of overdosage shown on the isodose contours. Fletcher and Stovall (1962) concluded that isodose contours should be made routinely through various planes of the implant and that dosage inhomogeneities should be sought and corrected during the time of treatment.

Due to the limitations of our radium needle stock (*e.g.*, lack of Indian Club needles and limited source strengths), isodose contours were performed on three typical planar implants used in our institution. From such contours, we hoped to recognize the geometrical patterns associated with either inadequate coverage of the lesion or areas of overdosage, or both, and to avoid these. Furthermore, we wanted to demonstrate the considerable influence of the location of the crossing needle on the area we routinely chose as the "treatment volume": an arbitrary choice of 85% of the maximal dose.

If one views the isodose distributions, one notes that:

(1) The area that receives 85% of the maximum dose reaches a maximum value as the crossing needle is moved beyond the active ends.

(2) To yield the largest 85% area, the crossing needle in all three cases should either be directly at or slightly beyond the physical ends.

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*T.N.M. staging system.

(3) The areas of highest dose (denoted by diagonal lines) decrease in intensity as the crossing needle is moved further away from the active ends.

(4) If the crossing needle is moved too far away from the physical ends, the isodose lines tend to move inward at the upper corners leaving these areas within the implant with a deficiency of dose.

(5) The 50% line represents essentially the same area in each type of implant, while the 85% line and the "hot spots" change significantly with different locations of the crossing needle.

It is important to note that only about two-thirds of the implant area is clinically useful.

In comparing the three implants, it is observed that while the 85% area remains large over a limited range of crossing needle positions, this range becomes more limited when one considers that the isodose distribution may become unacceptable for crossing needle positions near the active ends which yield areas of relatively high intensity, and for distant crossing needle positions which result in diminished dose in the upper corners of the implant.

With regard to the size and uniformity of the 85% area in relation to the physical dimensions of the implant, it is clearly seen that the Manchester geometry is superior to the other two. As Fig. 5 indicates, the 85% area covers a much larger fraction of the physical size of the implant over a wider range. Indeed, one may be inclined to favour this geometry because of its "forgiving" nature.

Paterson and Parker (1938) stated that the crossing needle of an interstitial implant should be placed not more than 1 cm away from the active ends of the needles. As a refinement to this rule, we suggest that the radiotherapist use the physical ends as the preferred position for the crossing needle. This general "rule of thumb" will allow for a larger and more uniform area of radiation over the area of the implant. While this is true for the examples we have given, we expect it to be true for all Paterson-Parker planar geometries.

Acknowledgments

The authors greatly appreciate the editorial assistance of Dr. R. O. Kornelsen of the A. Maxwell Evans Clinic, Vancouver, British Columbia. This report was first presented at the Regional Meeting of the American Association of Physicists in Medicine, Kansas City, Missouri, on February 11, 1978.

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Book review

Human brainstem vessels. By H. M. duvernoy, pp. xi+188, illus., 1978 (Springer Verlag, Berlin, Heidelberg, New York), DM290/$133.40.
ISBN 3-540-08336-7.

This book describes the arteries, veins and capillary network of the human brain stem in great detail.

It is divided into two parts. In the first the superficial segments of the vessels and their site of penetration into the tissue are described as well as their territories of distribution. It is superbly illustrated with photographs of specimens and colour coded diagrams.

The second part dealing with the internal capillary network of the brain stem is illustrated with thin sections taken in sagittal, coronal and transverse planes of brain stems in which the vessels have been injected with Indian ink.

This beautiful book is the product of an immense amount of work and it provides detailed information which is not available elsewhere. Its main interest will be to neuroanatomists, but it should be available for reference for neuroradiologists and other neurological scientists seeking highly detailed information on human brain stem vasculature.

B. Kendall.

1979, *British Journal of Radiology*, *52*, 816–821

Changes in the neuroglial cell populations of the rat spinal cord after local X-irradiation

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(*Received November 1978 and in revised form March 1979*)

ABSTRACT

A 16 mm length of cervical spinal cord of young adult female rats was irradiated with 4000 rad of 250 kV X rays. Counts of astrocyte and oligodendrocyte nuclei were made in the dorsal columns of both irradiated and control cervical cords during the latent period before the onset of radionecrosis.

The numbers of both astrocyte and oligodendrocyte nuclei were reduced one month after exposure to radiation. Both cell populations showed an apparent recovery but this was subsequently followed by a rapid loss of cells prior to the development of white-matter necrosis. The oligodendrocyte population in unirradiated spinal cords increased with age, and mitotic figures were observed among the neuroglia of both irradiated and control cervical spinal cords.

A slow, natural turnover of neuroglial cells in the cervical spinal cord is proposed and the relevance of this to the manifestation of delayed white matter necrosis is discussed.

There are many reports of white-matter necrosis developing in the spinal cord some months or even years after treatment of the cord with therapeutic doses of radiation (Smithers *et al.*, 1943; Boden, 1948; Greenfield and Stark, 1948; Pallis *et al.*, 1961; Dynes and Smedal, 1960). Radionecrosis of the spinal cord is therefore a matter of concern for radiotherapists treating tumours of the spinal cord and other closely situated tissues. The initial benefit obtained by treatment of a tumour may later be more than outweighed by necrosis of the normal nervous tissue, resulting in severe disablement or death.

The pathogenesis of delayed white-matter necrosis is not clear, but it has been proposed that cells with a slow turnover time may be involved and furthermore that the long life-span of such cells may account for the delayed onset of radiation myelopathy. Neuroglial and endothelial cells have been suggested as possible elements involved in the development of white-matter necrosis; however, the primary cell type affected has not been positively identified (Zeman, 1963; Kogel and Barendsen, 1974; Hopewell and Wright, 1975).

Local irradiation with single doses of 2200–4000 rad to the spinal cord of the rat produces myelopathy and histological evidence of white-matter necrosis (after a similar latent period of four to five months), over this entire dose range (Innes and Carsten, 1961; Hopewell and Wright, 1975; Kogel and Barendsen, 1974; Hubbard and Hopewell, 1978). The rat, therefore, is a suitable animal for an investigation of the pathogenesis of radiation-induced necrosis in the spinal cord.

In order to clarify the role of neuroglia in the manifestation of white-matter necrosis, changes in the astrocyte and oligodendrocyte cell populations of the rat cervical cord have been measured during the latent period prior to the onset of radionecrosis after a single dose of 4000 rad. The turnover of neuroglial cells in the same region of the cord has also been evaluated.

MATERIALS AND METHODS

Under chloral hydrate anaesthesia (300 mg/kg) the cervical spine cord of 12-week old female Sprague Dawley rats was irradiated with 4000 rad of 250 kV X rays at 116 rad/min (HVL 1.3 mmCu). A 16 mm length of the spinal cord was irradiated laterally using parallel opposed fields in a similar manner to that described by Carsten and Zeman (1966). The large spine of the second thoracic vertebra marked the posterior limit of the irradiation field. A group of age-matched animals was used as controls.

Six control animals were killed when 12 weeks old and thereafter further groups of six irradiated and six age-matched control animals were examined at monthly intervals after irradiation. Animals were killed under ether anaesthesia by cardiac perfusion with 1% glacial acetic acid in 10% formal saline (Cavanagh and Lewis, 1969). The vertebral column lying between the atlas and the fourth thoracic vertebra was removed. The cervical cord was then dissected from the vertebrae and the irradiated length or equivalent region of cord in control animals was cut transversely and longitudinally into four pieces (Fig. 1). These were processed using standard histological techniques. 5 μm sections of the tissue were stained with haematoxylin and eosin.

In addition a further six unirradiated rats of the same age and sex were given repeated intraperitoneal injections of tritiated thymidine (5 Ci/Mmol): 0.2 μCi per gram body weight was administered in 0.2 ml of normal saline every eight hours. At intervals of

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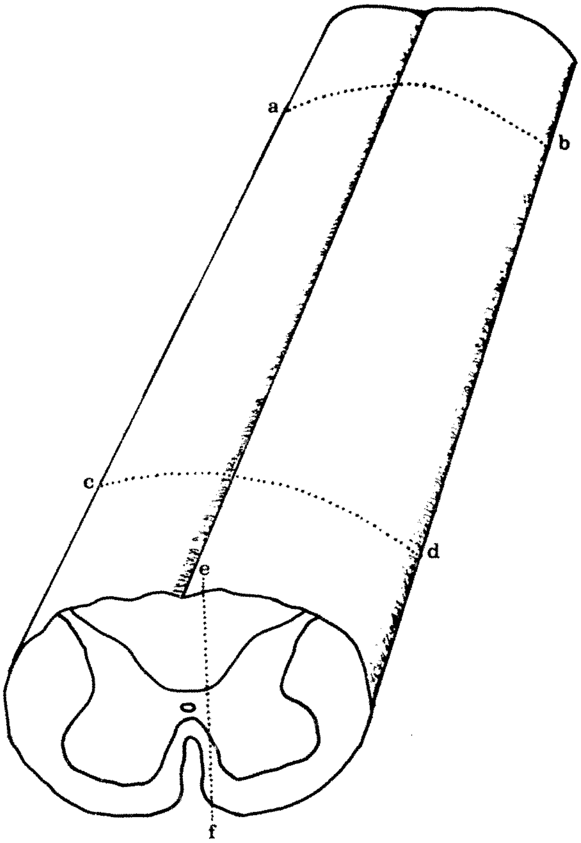

Fig. 1.

Diagram of the cervical cord demonstrating the method of dissection. Transverse sections of the cord were prepared from 2 mm lengths of the cord obtained by cutting at ab and cd. Longitudinal sections were obtained from the remaining 8 mm of the cord by cutting along the plane ef.

24 hours, one week and one month after the start of injections, pairs of rats were killed by cardiac perfusion. The cervical cord was dissected out and 5 μm sections prepared as described previously. Autoradiographs were set up using a stripping film technique (Rogers, 1973) and exposed at 4°C for six weeks. Following development they were stained with Mayer's haematoxylin.

Changes in the number of astrocyte nuclei in the dorsal columns of the spinal cord following local irradiation were determined from the transverse sections of the cord using an oil immersion objective (× 100 magnification) and a squared ocular grid (115 μm^2). Five distinct microscope fields were examined per section using the method of Cavanagh *et al.*, (1971). Ten sections of cord were assessed for every animal, five from each of the two transverse pieces cut from the cord (Fig. 1).

Associated changes in the number of oligodendrocyte nuclei in the same region of the spinal cord were determined from the longitudinal sections using an ocular grid (1270 μm^2) and a × 40 objective. Two histologically distinct areas were examined (Fig. 2), area A adjacent to the grey matter around the central canal where there are many long straight axons and area B directly beneath the meninges where the axons lie in many different planes. Five sections were assessed from each animal and ten successive microscope fields were examined for cell nuclei in both areas. Identification of the different cell types was carried out according to the criteria of Smart and Leblond (1961).

The autoradiographs were examined with an oil immersion objective (× 100 magnification) and the proportion of labelled neuroglia in both grey and white matter adjacent to the central canal was determined with the use of an ocular grid (115 μm^2).

Results

Figures 3 and 4 show the changes that occurred in the astrocyte and oligodendrocyte cell populations of the cervical cord following irradiation with a single dose of 4000 rad. Although there was a greater population of oligodendrocytes in the deeper region of white matter (area A) than in the more superficial submeningeal region (area B), the two populations behaved similarly in both irradiated and control spinal cords.

One month after exposure the numbers of astrocyte and oligodendrocyte nuclei were significantly reduced when compared with age-matched control animals ($P < 0.01$). Within two months of irradiation, nuclear density had returned to normal or was increased. This recovery, however, was of limited duration and three months after treatment all three cell populations examined were significantly reduced in number ($P < 0.01$). This decline continued into the fourth month after irradiation.

In control spinal cords, a steady rise in the number of oligodendrocyte nuclei was found with increasing age. The number of astrocyte nuclei, however, remained fairly constant in control animals over the period of this study. Mitotic figures were occasionally seen in both astrocytes and oligodendrocytes of the white matter in control and irradiated spinal cords. Some of the mitotic figures observed in irradiated cords were abnormal.

Evidence of white-matter necrosis was only observed in two of the six irradiated animals kept for four months after irradiation. The lesions were not extensive. Vascular damage was not observed at any time after irradiation and no animals developed

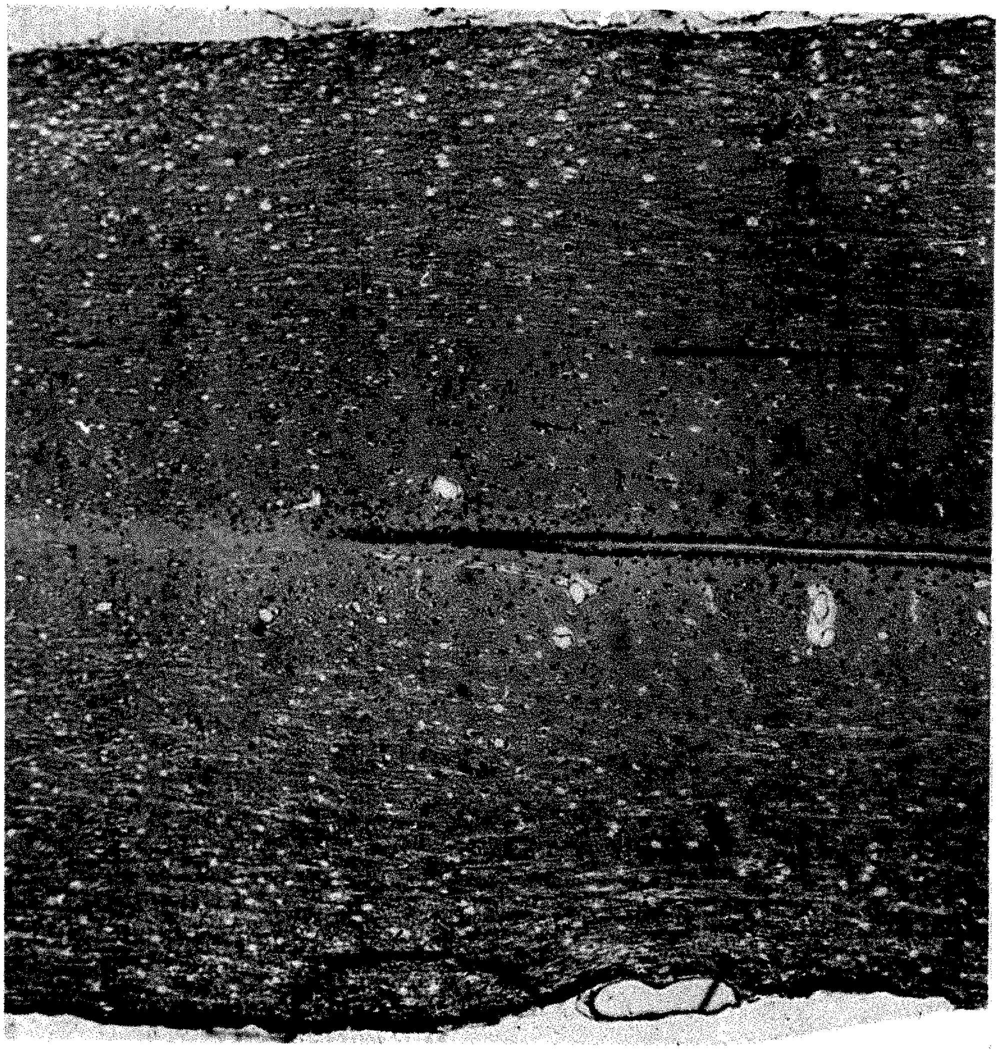

Fig. 2.

Longitudinal section of the cervical cord from a three month old unirradiated rat demonstrating the two histologically distinct regions (A and B) of oligodendrocyte cell density in the dorsal columns of the white matter (H & E × 75).

paralysis. This would suggest that a sudden onset of necrosis is associated with the rapid development of paralysis five to six months after irradiation.

Following repeated intraperitoneal injections of ^{3}H-thymidine there was a gradual increase in the percentage of labelled neuroglial nuclei in both the grey and white matter of the cervical spinal cord with time (Table I). However, the proportion of labelled cells was always greater in the white matter. One month after repeated injections of ^{3}H-thymidine there was a three-fold difference in the labelling index of neuroglia in these two regions of the cervical spinal cord.

TABLE I

THE PROPORTIONS OF LABELLED NEUROGLIAL CELLS OCCURRING IN THE GREY AND WHITE MATTER OF THE RAT CERVICAL CORD AT VARIOUS TIME INTERVALS AFTER REPEATED INJECTIONS OF ^{3}H-THYMIDINE

Duration of labelling with ^{3}H-thymidine	Labelling index %	
	White matter	Grey matter
24 hours	2.4% (1469)	1.5% (1775)
7 days	3.1% (1540)	1.9% (1888)
28 days	12.0% (1744)	4.4% (1833)

Figures in parenthesis show total number of cells counted for the determination of each labelling index.

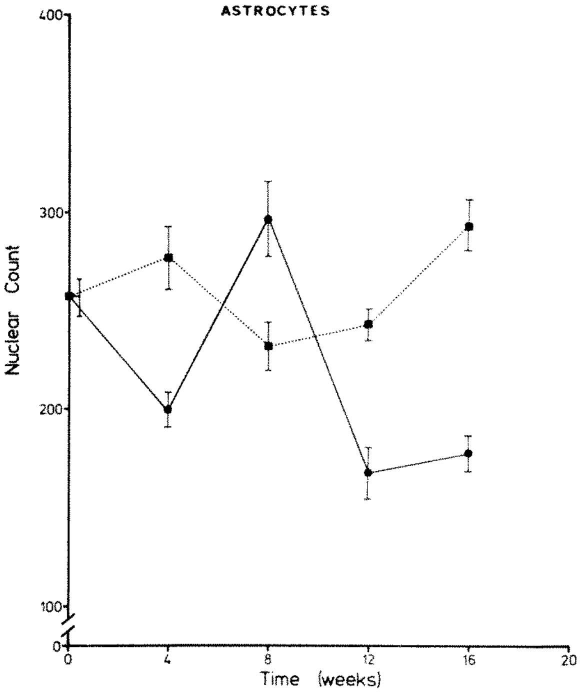

FIG. 3.

Changes in the numbers of astrocyte nuclei in the white matter of the cervical cord during the latent period for radionecrosis (■...... ■ control, ●——● irradiated 4000 rad).

DISCUSSION

Irradiation of the rat cervical spinal cord with 4000 rad of X rays resulted in a significant deficit of both astrocyte and oligodendrocyte nuclei three to four months after exposure. There was, however, a proportionately greater loss of oligodendrocytes (30–56%) than astrocytes (26%), the loss of oligodendrocytes being greatest in area A.

Myelination in the rat is complete by 30 days "post partum" (Davison *et al.*, 1966). Therefore the increasing population of oligodendrocytes observed in control cords and the occurrence of mitotic figures and labelled nuclei amongst the astrocytes and oligodendrocytes of both control and irradiated spinal cords suggest that, in the young adult rat, the glial cell population of the cervical spinal cord is not static. However, cell turnover cannot be rapid since the occurrence of abnormal mitotic figures as late as three to four months after local irradiation indicates that these cells are dividing for possibly the first time since exposure. The consistently higher labelling index in white matter compared with grey suggests that there is a greater turnover of glial cells in white matter than in grey.

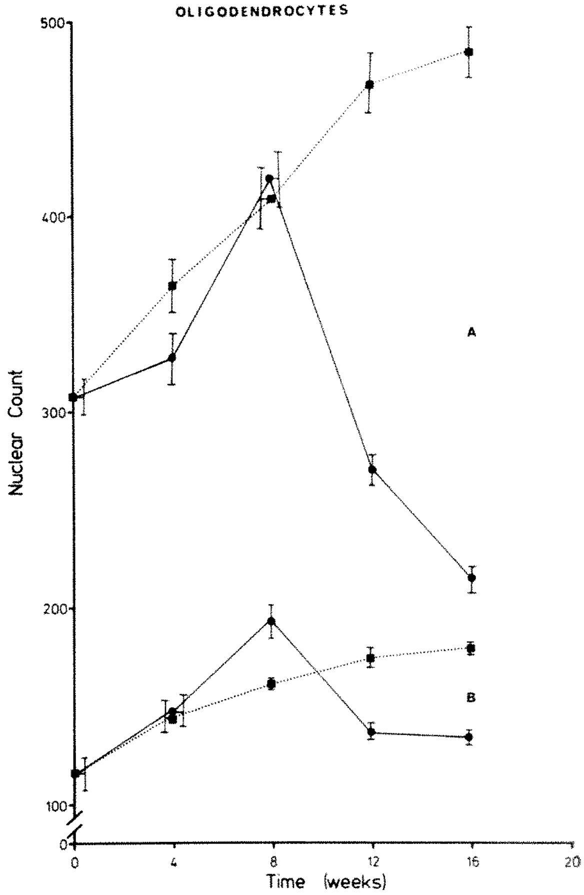

FIG. 4.

Changes in the numbers of oligodendrocyte nuclei in the white matter of the cervical cord during the latent period for radionecrosis (■...... ■ control, ●——● irradiated 4000 rad).

The transient rise in the glial cell population observed two months after treatment confirms a previous report by Zeman (1963) who described an increased number of glial cells in the white matter of the rat cervical cord three months after local irradiation with 3500 rad of X rays. Similarly, as these animals approached the expected onset of paraplegia the cell count decreased. Furthermore, Zeman established that there appeared to be a rapid loss of DNA-synthesizing cells just prior to the onset of paralysis since, following a single pulse of ^{3}H-thymidine, the labelling index of neuroglial cells in the white matter of irradiated animals fell from 10% three hours after labelling to 3% after three days. This cell loss, we would suggest, may be due to mitotic cell death. The labelling index found by

Zeman (1963) in control animals after a single pulse of ^{3}H-thymidine was similar to that in the present study.

In the absence of any obvious vascular lesions it is unlikely that the observed white-matter lesions result, at this level of radiation dose, from damage to vessel walls. However, in view of the distinct radiation response of neuroglia in both the present and a previous study (Zeman, 1963), it is proposed that radiation-induced white-matter necrosis results from a loss of neuroglia. Since the turnover of neuroglial cells appears to be slow, cell loss is gradual and initially insufficient to stimulate increased mitotic activity of the remaining neuroglia. However, many of the neuroglia are eventually stimulated into division in an attempt to repopulate the white matter and they undergo mitotic cell death due to prior radiation damage (Hopewell and Wright, 1970). The neuroglial cell population of the white matter then declines more rapidly, resulting in the sudden development of white-matter necrosis. The apparent higher rate of neuroglial-cell turnover in white than in grey matter could account for the selective damage to white matter. These proposals are consistent with previously reported investigations of white-matter radionecrosis in the spinal cord (van der Kogel and Barendsen, 1974; Hopewell and Wright, 1975).

A recent study with fractionated doses (van der Kogel, 1977) has shown that the spinal cord of the rat has a large capacity for the repair of sublethal damage. However, additional recovery was found after an interval of two months or more between fractions and this has been attributed to repopulation by cells with a slow turnover. This interval corresponds with the apparent recovery of both astrocyte and oligodendrocyte cell populations observed two months after irradiation.

Oligodendrocytes are responsible for the production of myelin in the CNS (Cruickshank *et al.*, 1968) and they are capable of carrying out remyelination in the cervical region of the spinal cord (Koenig *et al.*, 1962). Other autoradiographic studies are in agreement with those reported here and have shown that neuroglia have a slow turnover time (Zeman *et al.*, 1964; Korr *et al.*, 1973). A gradual loss of oligodendrocytes at cell division as opposed to any direct action of radiation would explain the evidence for nodal widening found in teased myelinated fibres from previously irradiated cervical cord (Mastaglia *et al.*, 1975). In addition, the present finding that the oligodendrocyte population of the cervical cord shows the greatest deficit just prior to the onset of paralysis would suggest that this is the primary cell type involved in the development of radiation-induced white-matter necrosis of the cervical cord.

Acknowledgments

The authors are endebted to Mrs. E. Whitehouse and Mrs. C. Hubbard for their careful preparation of the histological sections and to Mr. P. Thompson for the care of the animals. This study was supported by the National Fund for Research into Crippling Diseases to which one of us (B. M. H.) acknowledges personal support. The Churchill Hospital Research Institute is supported by a grant from the Cancer Research Campaign.

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Book review

Atlas of Abdominal Ultrasonography in Children. By Gary F. Gates, pp. xvii+283, 1978 (Churchill Livingstone, Edinburgh) £16·50.

ISBN 0443–08015–1

Ultrasound and paediatrics seem an obvious combination. The safety of ultrasound, the minimum preparation of the patient required and the ready acceptance of the technique by the patient are all special features of ultrasound which are particularly important when children require investigation. So it is somewhat surprising that the exploitation of ultrasound in this field has lagged behind other areas and for these reasons Dr. Gates's book is especially welcome.

As befits an atlas, it is a comprehensive survey of established applications of conventional ultrasonography, embellished with numerous examples of ultrasonic case reports. The newer real-time systems and the Octoson, both especially important in paediatrics, have been omitted. A general introduction deals with practical matters peculiar to paediatrics, such as methods of persuading the child to keep still and hints on how best to explain what is being done to the older child, often with refreshing practical touches such as advice to provide the child with a sample from the study or a "drawing" on the screen as a memento.

Each section has a concise introduction describing recommended scanning methods, merits of other imaging techniques compared to ultrasound, and an overview of the applications. Comprehensive coverage is given to the liver, with some unusual disorders such as glycogen storage diseases and diaphragmatic hernias, but with due emphasis of important, commoner conditions, such as abscesses and tumours. Disorders of the biliary tree are well described and documented, including a lucid description of the biliary atresias. Disorders elsewhere in the abdomen are also given wide coverage.

The section on the renal tract is a particularly excellent presentation of the gamut of congenital and acquired disease, concisely explained and well documented. A particular feature of Dr. Gates's presentation is the delineation of the particular and usually complementary roles of isotope and ultrasound scans. This multi-disciplinary approach to diagnostic imaging is well exemplified in this chapter which also includes references to conventional radiological techniques that are relevant. Imaging by computer assisted tomography is only referred to in the text but this is not a serious limitation in practice since CAT is not currently widely available for paediatric use.

A comprehensive "contents" does service for an index; coupled with a good internal cross reference system this is usually sufficient. Excellent references up to 1977 serve to direct further reading.

The complexity of diagnosis available from ultrasound is frequently noted and a sensible attitude that "the ultrasound examination must be closely correlated with the patient's clinical history in order to arrive at a reasonable diagnosis" is the voice of a seasoned practitioner. On occasion, however, the text is uncritical of the clinical usefulness of ultrasound examination. For example, although the demonstration of ureteric dilatation will distinguish lower ureteric from pelviureteric junction obstruction, the difficulty of imaging a moderately dilated ureter is not emphasized and so the significance of a negative observation escapes attention. Similarly, on occasion the ultrasonic features that would allow a differential diagnosis between confusing conditions is sometimes omitted. The reader might be led to believe that the ultrasonic features alone allow a confident distinction to be made between an upper pole renal cyst and an upper hydronephrosis in a duplex kidney.

However, these are minor reservations in an excellent text that will provide a valuable background for referring physicians and practising diagnosticians. Paediatric physicians, surgeons and radiologists will find it stimulating and informative.

DAVID O. COSGROVE.

1979, *British Journal of Radiology*, *52*, 822–825

Some radiobiological consequences of mycoplasma contamination of mammalian cells in tissue culture

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ABSTRACT

Cells of the mouse Ehrlich ascites carcinoma grown *in vitro* became contaminated with an arginine-splitting mycoplasma. The slopes of the radiation dose-survival curves of the contaminated cells, assayed by colony-forming ability, were extremely variable; eventually it became impossible to grow colonies at all. Experiments on the feeder cell requirement showed that, whereas for clean cells the maximum plating efficiency was obtained within a range of 5×10^4 and 4×10^5 feeder cells in a 5 cm dish, contaminated cells would only produce colonies in the presence of between 10^4 and 3×10^4 feeder cells. Doubling the concentration of arginine in the medium allowed contaminated cells to grow with maximum plating efficiency within an increased range of 10^4 and 4×10^5 feeder cells. The mycoplasmas were apparently behaving as feeders, reducing the requirement for added feeder cells, but also depleting the medium of essential arginine. The cells were eventually decontaminated by passing them through a mouse as an ascites tumour.

The purpose of this paper is to show that mycoplasma contamination of mammalian cells can distort the results of radiobiological experiments and also to demonstrate how the mycoplasma may produce its effect.

Mycoplasmas represent the smallest free-living organisms known at present. They are prokaryotic cells with a single lipoprotein membrane but no cell wall; they are usually between 0.2 μm and 0.5 μm in diameter but a small proportion of the population may be smaller than this and therefore able to pass through the normal 0.2 μm sterilizing filters. Mycoplasmas were first isolated from a culture of mammalian cells by Robinson and her colleagues (1956) and since then there have been frequent reports of contamination of mammalian cell cultures by these organisms (Rothblat and Morton, 1959; Pollock *et al.*, 1960; Barile *et al.*, 1962). There have also been reports of the effects of mycoplasma on various aspects of mammalian cell behaviour; some mycoplasmas inhibit cell metabolism (Hakala *et al.*, 1963), cell growth (Kenny and Pollock, 1963) and phytohaemagglutin stimulation of lymphocyte cultures (Barile and Leventhal, 1968), while others may alter nucleic acid synthesis (Stanbridge *et al.*, 1969), or cause chromosomal aberrations (Fogh and Fogh, 1965).

MATERIALS AND METHODS

The mammalian cells used were those of the Ehrlich Landschütz mouse ascites carcinoma, grown *in vitro* as a monolayer culture. Growth medium was Eagle's M.E.M. (Wellcome) with 15% fetal calf serum plus penicillin (500 units/ml), streptomycin (0.5 mg/ml) and mycostatin (100 units/ml). Single cell suspensions were prepared from monolayer cultures with 0.1% trypsin. Cells surviving experimental treatments were assayed by their ability to form colonies in 5 cm polystyrene Petri dishes to which feeder cells had been added. The feeder cells were cells of the same strain which had received 40 Gy of X rays; they were plated the day before the test cells were added.

The experiments which were in progress at the time the mycoplasma contamination became apparent involved the production of X-ray dose-survival curves and the usual way of obtaining these was to add 10^5 feeder cells in 3 ml of medium to each Petri dish, to incubate overnight and the following morning to add graded numbers of test cells to the dishes according to the dose of X rays to be given. The test cells were allowed to attach for 4 h, the medium was removed and the dishes were irradiated; 8 ml of medium was then added to each dish and they were incubated undisturbed for 10 days for colony formation.

RESULTS

Variability of survival curves

Before the mycoplasma problem arose, dose-survival curves on a semi-log plot of cells irradiated in air had a small shoulder followed by a straight exponential region which had a D_0 of about 1.70 Gy. The behaviour of the cells in this respect then became extremely unpredictable; D_0 values as low as 0.65 Gy were measured and continuously bending survival curves were sometimes obtained. On some occasions it was impossible to grow any colonies at all although routine cultures appeared to be growing normally. The cells were tested on two

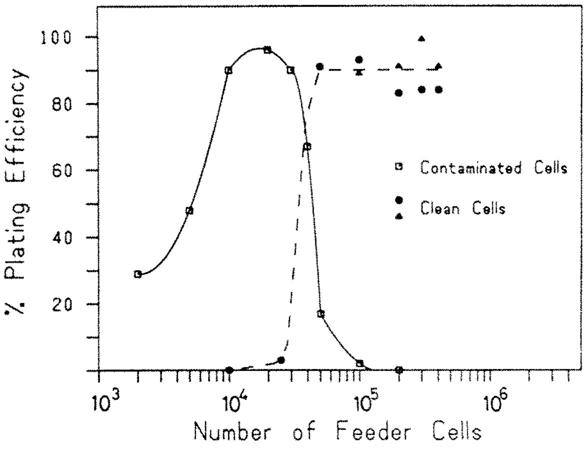

FIG. 1.

Difference in number of feeder cells required for maximal plating efficiency of clean and contaminated cells.

occasions for mycoplasma contamination but because neither test gave a positive result the source of the problem was erroneously assumed to lie elsewhere.

Change in the feeder cell requirement of contaminated cells

The mouse cells used in these experiments will produce colonies from low numbers of single viable cells only if feeder cells are present. In Fig. 1 it can be seen that before the cells became contaminated the maximum plating efficiency was obtained when between 5×10^4 and 4×10^5 feeder cells were present; therefore in all survival curve experiments 10^5 feeder cells were added to each dish followed by graded numbers of test cells depending on the radiation dose to be given, with a maximum of 10^5 cells for the high doses of radiation. It was felt that with a total cell number in the range of 10^5–2×10^5 it was safe to assume the maximum plating efficiency on each dish. At the time when it became difficult or impossible to grow colonies by this technique, the range of the optimum number of feeder cells was redetermined and the result can also be seen in Fig. 1. The previous optimal range of 10^5–2×10^5 now produced almost zero plating efficiency and there was a precarious plateau of maximum plating efficiency when between 10^4 and 3×10^4 cells were present.

Experiments on the growth rate of various numbers of the cells in Petri dishes showed that, although their initial doubling time was 16 h, growth ceased after 4–6 days depending on the initial number of cells present. Because the cells still had plenty of space, failure to grow suggested that premature depletion of the medium could be the cause of the problem. Samples of growth medium were supplemented with either glutamine, vitamins or essential amino-acids and the plating efficiency of cells on various numbers of feeder cells determined. Addition of essential amino-acids restored the maximum plating efficiency in the region of 10^5 feeder cells and tests on individual essential amino-acids showed that l-arginine was the effective component; 0.6 mM arginine added to the medium extended the range of feeder cell numbers, yielding maximum plating efficiency from 10^4 to more than 4×10^5.

The finding that there was insufficient arginine in the medium again raised the possibility of mycoplasma contamination because some common strains of mycoplasma contain an arginine deiminase which converts the arginine essential for mammalian cells into citrulline. The cells were tested for mycoplasma by Dr. Taylor-Robinson who reported heavy contamination with an arginine-splitting mycoplasma, which proved difficult to identify but was probably *M. arginini.*

Decontamination of the mammalian cells

In vitro cell cultures contaminated with mycoplasma are notoriously difficult to "clean"; one possibility was to passage the cells intraperitoneally through a mouse in the hope that the mouse's immune mechanisms would remove the mycoplasma. Approximately 4.5×10^6 contaminated cells were injected *I.P.* into a mouse which, in ten days, produced an ascites tumour containing about 10^9 cells. This tumour was serially passaged through five mice by transfer of 0.1 ml of ascites tumour *I.P.* after ten days' growth. After two further *in vitro* subcultures the cells were again tested for mycoplasma by Dr. Taylor-Robinson who found no contamination. Maximum plating efficiency was achieved in the presence of $10^5-4\times10^5$ cells and "straight" survival curves with a D_0 of about 1.70 Gy were obtained using normal growth medium.

The mouse cells have since been cultured *in vitro* using rigid sterile techniques, almost always without antibiotic, for the past three years; cultures have occasionally been discarded because of bacterial contamination but there has been no further infection with mycoplasma, judged by monthly mycoplasma screening and the reproducibility of experimental results.

DISCUSSION

Mycoplasma have been shown to be common contaminants of mammalian cell cultures (Barile *et al.*, 1962), so it is surprising that only one report of the effect of mycoplasma contamination on the radiobiological properties of mammalian cells has been published (Pritchard and Moore, 1971). These authors found that two contaminated strains of HeLa S_3 cells had lower D_0 values than an apparently uncontaminated one. Any contaminant depleting the medium of arginine or some other vital metabolite could produce an apparent decrease in D_0 for the following reason. In experiments to measure survival curves it is usual to grade the number of cells put into a standard volume of medium in a Petri dish according to the dose of radiation to be given, more cells being used at high than at low dose levels so that similar numbers of survivors are left on each dish. The range of cell numbers for which this procedure is justified can be determined (c.f. Fig. 1). However, if the cells become contaminated with mycoplasma the situation may change because the high dose dishes contain (a) more metabolizing cells, because radiation-killed cells remain metabolically active for some time after irradiation, and (b) probably more mycoplasma associated with the greater number of of test cells, so there is a likelihood that cells surviving the high dose of radiation will suffer depletion of the medium to a greater extent than those surviving low doses. If such depletion prevents some cells which survive the radiation from developing into colonies of scorable size, the resulting survival curves will be steeper and the D_0 values correspondingly lower than those obtained for uncontaminated cells. This seems to be the most likely explanation of the variability in D_0 found with contaminated cells.

Mycoplasmas may have some capacity for behaving as feeders for mammalian cells. In Fig. 1 it can be seen that when the cultures were contaminated only 10^4 feeder cells were required for maximum plating efficiency whereas more than twice this number were required for uncontaminated cells. The minimum number of feeder cells producing maximum plating efficiency was not altered by the addition of arginine to either contaminated or "clean" cultures.

The mycoplasma contamination was eventually detected from the additional arginine requirement of the cells. However, not all mycoplasmas have a requirement for arginine; some species metabolize glucose, others urea, so it is important to be sure that all types can be detected in any screening procedure. Modifications of Hayflick's medium (Hayflick, 1965) have been described which can be used to detect arginine-splitting and glucose-fermenting mycoplasmas (Manchee and Taylor-Robinson, 1968). Urea-splitting mycoplasmas can be detected by inoculating into liquid medium (Manchee and Taylor-Robinson, 1968) containing 0.025% thallium acetate and 0.1% urea, with the pH adjusted to 7.0 with NHCl (Taylor-Robinson, personal communication). Colour changes of the phenol red in the medium are indicative of mycoplasma contamination; urea and arginine-splitting species produce an increase in pH, and glucose-fermenting mycoplasmas a reduction.

Many of the ways in which mycoplasma can alter cell function have been described (Barile, 1973; Kenny, 1973). In the words of Barile, "The investigator must remain cognisant of mycoplasmas and their properties, and must maintain a constant surveillance for mycoplasmal contamination in order to interpret properly the result of his study".

ACKNOWLEDGMENTS

We are most grateful to Dr. D. Taylor-Robinson and Miss P. Furr (Clinical Research Centre, Northwick Park) and Dr. H. Danpure for their help in detecting mycoplasma and to Dr. S. Hornsey for her advice.

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Book review

Table of Isotopes. 7th edn. Edited by C. Michael Lederer and Virginia S. Shirley. Principal authors: Edgardo Browne, Janis M. Dairiki, Raymond E. Doebler. Authors: Adnan A. Shihab-Eldin, Leslie J. Jardine, Jagdish K. Tuli, Audrey B. Buyrn. pp. 1523, with introduction pp. 20, appendices and references pp. 76, 1978 (John Wiley & Sons Inc., New York, Chichester, Brisbane, Toronto), £28·00 (hard cover).
ISBN 0–471–04179–3
0–471–04180–7 (paperback).

"It is expected" write Lederer and Shirley in their preface "that the 7th edition of the *Table of Isotopes* will be the last in the series started in 1940." One can understand their feelings and the strength of their charming dedication to the children of editors and principal authors "who struggled with us throughout the compilation of this book and rejoiced with us upon its completion."

That first of the series, published in 1940 in the admirable "Reviews of Modern Physics", had just 17 pages. It was preceded by a three page listing by Livingston and Bethe in 1937 of induced radioactivities naming about 190 isotopes.

The 6th edition, of 1967, the first in the series not issued through "Reviews of Modern Physics", had 594 pages and comprised two major sections, one giving much simplified decay schemes with associated data and references (in a form similar to that used in the earlier tables), the other a critical analysis of each nuclide, with detailed energy level schemes.

In this massive (3 kg) edition, from the Lawrence Berkeley Laboratory, this subdivision has been abandoned. A simplified so-called mass chain decay scheme is given for each mass number, the associated pages containing a critical presentation of the data available for each nuclide. These data include both those associated with radioactive decay and all the energy levels found by nuclear spectroscopists. The editors explain in considerable detail in their 20 page introduction the policies adopted in selecting data and the notations used. This indeed is no table, it is an encyclopaedia. Throughout, emphasis is on experimental observations and their interpretation by the experimenters; "cut off dates" lie between January and December 1977.

In addition to the data on (so the publishers claim) 2600 isotopes, there are associated appendices giving, *inter alia*, constants and conversion factors; standards for nuclear spectroscopy; γ-ray and α-particle energies and electron intensities; atomic levels; data on absorption of radiation.

Clearly the driving force behind this book has been a wish to bring together a critical assessment of all the available data, with the primary aim of providing a source book for those concerned with the interpretation of nuclear structures; indeed the editors point out that the compilers of earlier editions were themselves often the authors of important discoveries and the compilations themselves led to new concepts of nuclear structure.

This brief résumé of the contents will indicate that this *Table of Isotopes* differs profoundly from earlier editions—certainly from editions 1–5—where chief attention was directed to the decay schemes of radionuclides. Here the radioactive properties are embedded in the extensive data on excitation energy levels. Furthermore, data on X-ray and Auger electron emission have to be derived from separate tables appearing in appendices. Although an excellent source book, the volume is certainly not designed for direct use by those primarily concerned with the applications of radioactivity to medicine or to other fields. The approach adopted in another series, beginning with "Radiations from Radioactive Atoms in Frequent Use" by Slack and Way (1959) and leading on to Dillman and Von der Lage (1975) in which emphasis is directed primarily to the radiations emitted including characteristic X rays and their absolute intensities, remains of chief direct value to the clinical user of radionuclides; the data used in these texts is, however, frequently drawn from the most recent edition of the *Table of Isotopes* and no doubt future versions of "Radionuclide Decay Schemes and Nuclear Parameters for use in Radiation Dose Estimation" (Dillman and Von der Lage, 1975) will draw heavily on this latest and possibly last edition.

The book is graced by a preface in which personal acknowledgment is made to those many people and institutions whose support was needed. A compliment is also paid to the helpful computers which, it appears, "entered, edited, stored, checked for form and consistency, formatted and finally typeset" or drew the material. The computers were also "educated to spot errors of form or consistency and violations of the laws, conventions and probabilities of physics". At the same time, as the editors rightly claim, the work has resulted in a production which has a quality much closer to traditional composition than to computer print out. (I was puzzled on the copyright page by the curious reference to its citation in the Library of Congress Catalogue as "Table of Isotopes. Sixth Ed. by C. M. Lederer, J. M. Hollander and I. Perlmann." Did the computer hiccup?).

The authors cite Rutherford as saying that the atomic emission spectrum of iron resembled "a grand piano falling down the stairs" and add that "the remarks of some contemporary physicists about complex decay schemes are unprintable".

This excellently produced volume will undoubtedly serve as a source book for many years and will find a place in most libraries with interests in nuclear physics throughout the world. Those involved in clinical work with radionuclides will find the book of value when they become interested in radioisotopes not already dealt with in the more medically directed tabulations, but otherwise are more likely to be daunted by the sheer weight of the information provided. The book is, nonetheless, superb value for its price.

N. G. TROTT.

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Skin and gonadal dose reduction during hip radiography of the bull

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ABSTRACT

Radiology is being used to an increasing extent in the clinical diagnosis of hip lameness in bulls. Consequent gonadal doses may have important implications in later breeding programmes. Skin and gonadal doses were recorded during hip radiography of 18 bulls. An additional 0.13 mm copper filtration reduced skin dose by more than one third, but had no effect on gonadal dose. The average radiation dose to the gonads was approximately halved by completely surrounding the scrotum with lead sheeting 0.95 mm in thickness.

Radiography has been used to confirm a clinical diagnosis of hip lameness in cattle (Weaver, 1969; Wood *et al.*, 1974a; Wood and Reynolds, 1975). In a preliminary investigation, Wood *et al.* (1974b) recorded radiation doses to the skin of 140–155 rad and to the gonads of 0.25–1.70 rad during hip joint radiography of four bulls. The aim of the present study was to examine the effect of additional copper filtration on radiation doses to the skin and gonads and the effect of lead shielding on gonadal dose.

MATERIALS AND METHODS

Eighteen bulls, varying in breed, age and weight, were presented for hip-joint radiography (Table I). Each bull was premedicated with xylazine and anaesthesia was induced with thiopentone sodium and maintained with halothane. The bulls were placed in dorsal recumbency on a mobile X-ray table with the stifle joints flexed and abducted (Figs. 1 and 2). The scrotum was reflected cranially and the centering point for the X-ray beam was marked with ink on the skin. The caudal surface of the scrotum then became the surface closest to the X-ray tube.

The production of a diagnostic X-ray film of the bovine hip requires large X-ray exposures. These ranged from 75 kV and 400 mAs for a 210 kg bull up

TABLE I

DETAILS OF 18 BULLS RADIOGRAPHED

Bull No.	Breed	Age (yr)	Weight (kg)	Tissue thickness (cm)	Anode skin distance (cm)	Exposure factors kV	Exposure factors mAs
79	Hereford	0.6	210	34	40	75	400
00	Hereford	1.5	480	39	41	95	600
H6	Hereford	2	490	42	38	95	1,200
92	Hereford	3	590	44	36	95	1,000
70	Hereford	3	660	46	36	115	1,500
13	Hereford	4	730	42	38	110	900
B3	Hereford	5	770	44	36	120	1,000
76	Hereford	5	770	43	37	115	900
83	Hereford	5	820	40	40	105	600
51	Hereford	5	770	45	40	115	1,500
16	Angus	5	640	39	41	95	600
15	Angus	6	600	42	41	105	1,500
12	Angus	6	600	38	40	105	1,500
11	Angus	7	610	42	42	105	1,500
C6	Charolais	2	800	47	37	120	1,200
93	Charolais	3	840	46	34	115	1,500
56	Friesian	2.5	630	41	37	95	1,200
97	Braford	5	640	44	36	95	800

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to 115 kV and 1500 mAs for an 840 kg animal. The heat generated at the anode following each X-ray exposure was such that an interval of about 10 min was required between subsequent exposures to permit time for the anode to cool. The time interval between X-ray exposures prolonged the length of general anaesthesia. Therefore it was only possible to study the effect of a single variable with any one animal. A different group of bulls was used for the study of each variable.

The thickness of tissue radiographed and the anode-skin distance were recorded. The anode film distance for each bull was approximately 80 cm. The selected exposure factors produced films of good diagnostic quality of both hips using screen film with high speed intensifying screens and a stationary grid having 48 lines per cm and a 12:1 ratio. The X-ray beam was reduced to the minimum practical size using a light-beam diaphragm. At all times the gonads were outside the primary X-ray beam.

Lithium fluoride thermoluminescent dosemeters (TLD)* were used to record radiation doses during each radiographic exposure. Forty mg of TLD powder was placed in a gelatin capsule. Two capsules were attached by adhesive tape to the skin in the centre of the primary X-ray beam. The average radiation dose to the pair of TLD's was expressed in rad in tissue per X-ray exposure and represented the skin dose.

Gonadal dose was measured using two pairs of TLD's, one pair on the cranial aspect, the other on the caudal aspect of the scrotum, at the level of the head of the right epididymus. The doses received on the cranial and caudal aspects were averaged and expressed as the average gonadal dose.

Measurements of skin and gonadal doses were made with a filter of 2.6 mm aluminium or with a combined filter of 1.13 mm copper and 2.6 mm aluminium. The copper was placed closest to the anode so that the aluminium absorbed the copper fluorescent radiation. Gonadal doses were recorded on some occasions with the scrotum unshielded and others with a gonadal shield of 0.95 mm lead placed either over the caudal aspect (tube side) of the scrotum or completely around the scrotum.

The results were analysed using a Chi-squared factorial experiment for the effect of copper filtration on gonadal dose and a stepwise multiple regression (Nie *et al.*, 1970) for the effects of gonadal shielding.

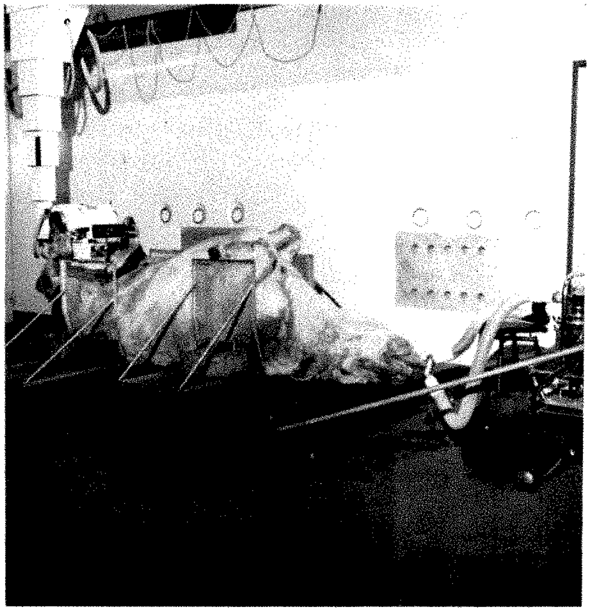

Fig. 1.

The bull has been anaesthetized for radiography and is positioned in dorsal recumbency on a mobile X-ray table.

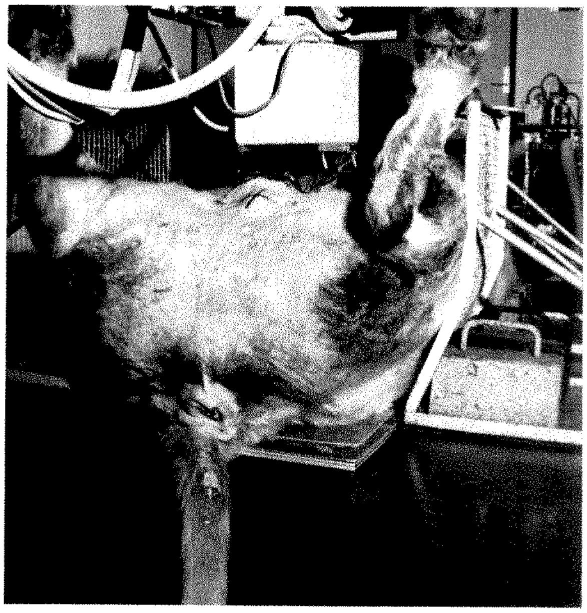

Fig. 2.

For hip radiography the stifle joints are flexed and abducted, and the scrotum is reflected cranially. The cassette has been positioned under the animal. The light-beam diaphragm is almost touching the skin. (In this photograph a coned-down view of the left hip is being taken. Two stationary grids with their grid lines at right angles have been placed on top of the cassette.)

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*TLD-100—Harshaw Chemical Company, Cleveland, Ohio, USA.

Results

The addition of a 0.13 mm copper filter reduced the skin dose by an average of 38.5% (See Table II). The skin dose for a single X-ray exposure ranged from 96 to 300 rad for aluminium filtration alone and from 61 to 196 rad for aluminium and copper.

With a 0.95 mm lead gonadal shield on the caudal aspect (tube side) of the scrotum, there was no reduction in gonadal dose when 0.13 mm copper was added at the tube port (Table III). The radiation dose recorded on the cranial aspect of the scrotum was significantly higher than that recorded on the caudal surface ($P < 0.025$).

TABLE II

Effect of 0.13 mm additional copper filtration on skin dose (rad)

Bull No.	2.6 mm Al filter	2.6 mm Al and 0.13 mm Cu filter	Percentage reduction
11	96	61	36
12	104	52	50
15	103	63	36
51	130	81	38
93	245	164	33
70	300	196	35

TABLE III

Effect of 0.13 mm additional copper filtration on gonadal dose (rad)

Mean of measurements from 5 bulls* with a 0.95 mm lead gonadal shield on the caudal aspect (tube side) of scrotum

Added filter	Cranial aspect of scrotum	Caudal aspect of scrotum	Average gonadal dose
Al†	1.77	1.22	1.50
Al and Cu‡	1.82	1.25	1.54

*Bulls radiographed were 12, 15, 51, 70 and 93
†2.6 mm additional aluminium filtration at the tube port
‡2.6 mm aluminium and 0.13 mm copper additional filtration at the tube port.

TABLE IV

The effect of shielding on gonadal dose (rad)

Mean of measurements from 13 bulls with 2.6 mm Al and 0.13 mm Cu additional filtration at the tube port

Gonadal shielding (0.95 mm lead)	Number of bulls	Cranial aspect scrotum	Caudal aspect scrotum	Average gonadal dose
No lead	9†	0.85	0.89	0.87
Lead on caudal aspect (tube side)	6‡	0.93	0.58	0.76
Lead surrounding scrotum	11§	0.35	0.46	0.40

†Bulls radiographed were 00, 13, 16, 76, 83, 92, 97, B3, C6
‡Bulls radiographed were 00, 56, 79, 93, 97, H6
§Bulls radiographed were 13, 16, 56, 76, 79, 83, 92, 93, B3, C6, H6

The analysis of measurements of radiation dose to the cranial and caudal aspects of the shielded and unshielded gonads of 13 bulls showed that there were significant differences in the radiation dose recorded ($P < 0.001$) (Table IV).

There were significant reductions ($P < 0.001$) in gonadal doses when 0.95 mm lead sheeting was placed either completely around the scrotum or over the caudal aspect (tube side) of the scrotum. Shielding completely around the scrotum resulted in a mean reduction in gonadal dose of 0.5 rad when compared to doses recorded without shielding. A gonadal shield on the caudal or tube side did not lead to a reduction in dose to the cranial aspect of the scrotum, but did lead to a mean reduction of 0.3 rad to the caudal aspect.

When a gonadal shield was placed over the caudal or tube side a significantly higher ($P < 0.05$) radiation dose was recorded on the cranial aspect than the caudal aspect of the scrotum. No significant differences were found in doses on the two aspects when either shielding was not present or lead was completely around the scrotum.

Discussion

The International Commission on Radiological Protection (1977) has stated that "the deleterious effects caused by irradiation of the gonads may be of three different types: tumour induction, impairment of fertility in the irradiated individual, and hereditary effects in descendants". It indicates that permanent impairment of fertility in human males is unlikely to occur unless doses of 250 rad or more are received at a high dose rate. It further indicates that hereditary effects that follow irradiation of the gonads are not likely to have a threshold and that in man the total risk of serious hereditary ill health is about 1 per 5000 offspring per rem of dose delivered.

The International Commission on Radiological Protection (1977) has further indicated that for human beings, skin is thought to be much less liable to develop fatal cancer after irradiation than most other tissues. It suggests that cosmetically-unacceptable changes in the skin may occur after irradiation with absorbed doses of 2000 rad or more, delivered over reasonably short periods. We have considered the magnitude of the doses reported in this paper in the light of these observations with regard to man.

When a 0.13 mm copper filter was added to 2.6 mm aluminium filtration at the tube port, the radiation dose to the skin in the centre of the primary X-ray beam was reduced by more than one third. There was no reduction in gonadal dose when the copper filter was added. The addition of copper filtration did not require an increase in the exposure factors and the diagnostic quality of the radiographs was maintained.

The observations of the International Commission on Radiological Protection (1977) with regard to effects in skin of human beings may not be applicable to bulls; however, they suggest that the skin doses reported here are not of great concern. Nevertheless we have shown that skin dose can be significantly reduced by use of an additional copper filter, at least 0.1 mm in thickness, and we consider this to be a desirable precaution.

The genetic significance of the gonadal doses will depend upon the future breeding life of the animal. Young bulls may be radiographed to detect evidence of a congenital degenerative arthropathy of the hips. Such changes may lead to a recommendation that the bull be slaughtered. A bull in a commercial herd in Australia has an average breeding life of three-and-a-half years and is usually culled from the herd at about five-and-a-half years of age. It is possible that during this time additional radiographs may be required to assess the progress of any radiological changes.

As the gonads were outside the primary X-ray beam the radiation dose recorded at the scrotal surface could have originated from several sources. A proportion of the radiation dose would have originated from the tube as penumbral or leakage radiation. Another source of radiation would be photons scattered by the animal's tissues.

In this study the most effective method of reducing gonadal dose was to surround the scrotum completely with 0.95 mm lead sheeting. The average radiation dose to the gonads was then approximately half the dose recorded in the same animal when gonadal shielding was not present. With the gonadal shield placed over the caudal aspect (tube side) of the scrotum the average reduction in gonadal dose was much smaller, being less than 13%. Also a significantly higher dose was recorded on the cranial than the caudal aspect of the scrotum. This suggests that the radiation dose received by the gonads had originated principally from photons scattered by the animal's tissues.

We conclude that in hip radiography of the bull:

(i) in all cases care should be taken to exclude the testes from the primary X-ray beam;

(ii) the number of radiographs taken of the hips of bulls to be used in a breeding programme should be reduced to a minimum. A full radiographic examination should be limited to a total of three films, one to include both hips, and the others coned-down films of each joint;

(iii) it is prudent to adopt effective low-cost methods of reducing the dose to the testes even though they are excluded from the primary X-ray beam. Completely surrounding the scrotum with lead sheeting of about 1 mm thickness was found to be an effective method of reducing gonadal dose.

ACKNOWLEDGMENTS

The statistical analysis of our results was carried out by Mr. R. M. Cannon. We gratefully acknowledge his advice and assistance. We also thank Dr. W. T. Reynolds and Dr. Barbara Vanselow for anaesthetising some of the bulls.

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Technical notes

Aids for use with EMI CT5005 general purpose scanner in tumour localization for radiotherapy treatment planning

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The clinical advantages of computed transverse axial tomography in the localization of tumours are well established. Radiotherapy treatment planning requires information in a form not usually presented by the EMI scanner. This paper describes some technical aids for use both in scanning and viewing procedures which overcome these shortcomings.

Couch design

If localizations are undertaken for the purpose of treatment planning it is necessary to reproduce the position of the patient during treatment. Geise and McCullough (1977) mentioned the contour distortion arising from couch design. The couch fitted as standard consists of a curved wooden pallet which runs in a trough on its support assembly. Fullerton *et al.* (1978) used the flat-topped couch of the Acta 0100 scanner to make the position of the patient compatible with that on most modern therapy units. A new flat-topped couch mentioned by Westbrook *et al.* (1978) and used in conjunction with the prototype EMIPLAN radiotherapy planning system installed at the Royal Marsden Hospital, Sutton branch, is illustrated and appears on several scans in a paper by Husband *et al.* (1978) but is not described.

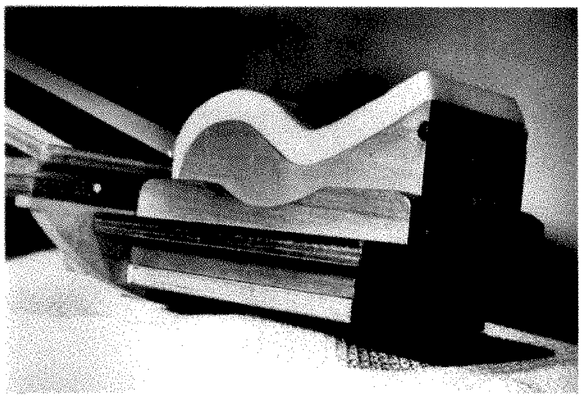

Fig. 1a.

Couch accessories showing head support asssembly, flat couch top, and tilting top.

At the Queen Elizabeth Hospital a flat couch top has been constructed out of 1.5 cm thick plywood, 183×31 cm (Fig. 1). It has three curved supports which match the curvature of the existing couch. All joints are dowelled, as metal screws or nails will cause ranging defects in the scans. To enable adjacent scans to be related to one another, five grooves, each 0.5×0.5 cm in cross-section, have been cut

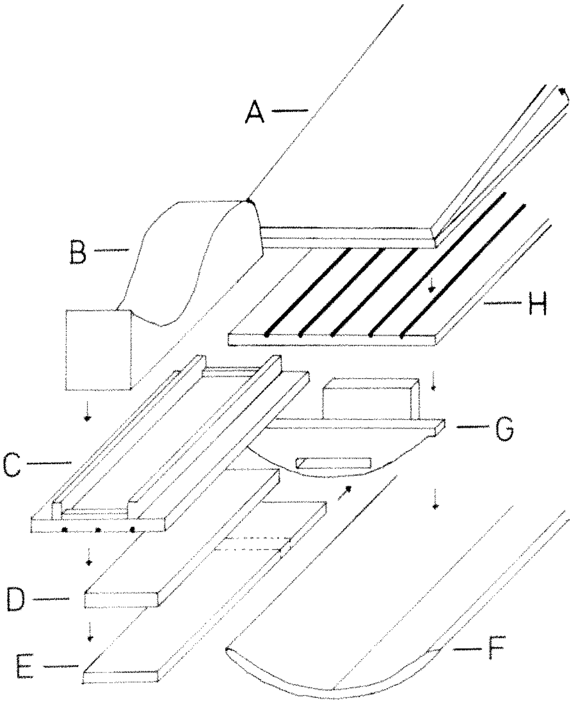

Fig. 1b.

Exploded view:
A—tilting couch top.
B—foam-covered head curve.
C—baseboard for attaching beam direction shells (Stent's compound marker strips on underside).
D—flat support spacer, variable height achieved by varying thickness (wedged spacers used when tilting couch top for angled scans).
E—baseboard support.
F—standard EMI scanner couch.
G—shaped support.
H—flat couch top (Stent's compound marker strips on upper side) can be used alone or with tilting top.

along the whole length of the couch top at 5 cm spacing and these have been filled with Stents' compound, a dental resin-wax composition material with an EMI number of approximately 270. These can clearly be seen on the scan and give an approximate scale as well as assisting in alignment (Fig. 2). With the flat couch top in position the uppermost surface of a patient with AP separation up to 26 cm is included in a 32 cm diameter scanning field. The couch top also incorporates a variable height head support assembly with the same basic design features as those used on our radiotherapy treatment couches. This has three strips of Stent's compound incorporated in it with a 5 cm spacing (Fig. 1B).

Bolusing

The distortion of surface contour caused by "bean bag" tissue compensators referred to by Geise *et al.* (1977) and Fullerton *et al.* (1978) makes determination of tumour position relative to surface markings inaccurate. Bolusing was deliberately omitted and a strip of Stent's compound 0.5×0.5 cm in cross-section was attached as a marker on the patient surface, parallel to the long axis of the body, in a position established by conventional radiography. Consequent loss of surface detail was minimal in most cases and the position of the relevant reference points remained clearly visible (Fig. 2). When localization scans were done in beam direction shells the rigidity of the cellulose acetate of which the shells were constructed made bolusing possible without appreciable distortion.

Stent's compound is mouldable at 60°C and, after immersion in warm water, strips can be moulded to fit the most uneven contours. It replaces the lead markers used in conventional radiographic localizations, providing sufficient contrast but not having an absorption outside the range of normal tissue.

Photo-optical transfer

The problems of photo-optical transfer of CT images have been mentioned by Fullerton *et al.* (1978). Any barrel distortion of the camera is intended to be corrected by the pin-cushion distortion of the video display, but the resultant image still exhibits some pin-cushion distortion.

A geometric phantom consisting of 0.173 mm diam (37 swg) copper wires spaced 2 cm apart in a water phantom was scanned and transparencies of the resultant image reproduced with each series of localization scans as a guide to both magnification and distortion (Fig. 3). The position of the wires was checked using the line printer output of EMI numbers provided as a routine option on the CT5005 scanner.

Both optical distortion and magnification were found to be different on the operator's console and the independent viewing console and each console exhibited variations from day to day.

Viewing

Transparencies were produced on Kodak nuclear medicine SO-179 film using a Shackman M6 Super Seven camera with M6 multi-position module back. This produced six images on a 25×20 cm (10×8 inch) film.

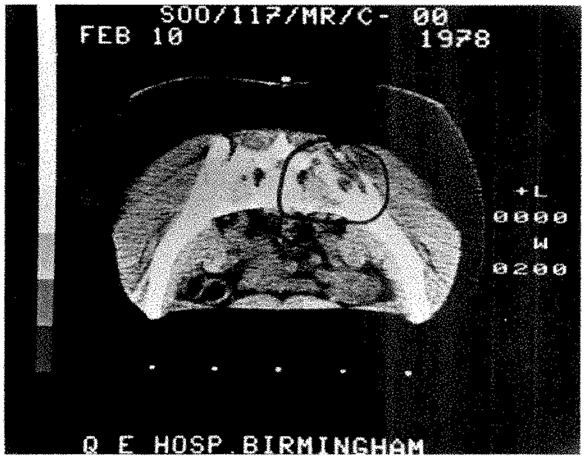

FIG. 2.
Localization scan of chordoma or right sacrum, patient prone, showing surface marker and couch top markers.

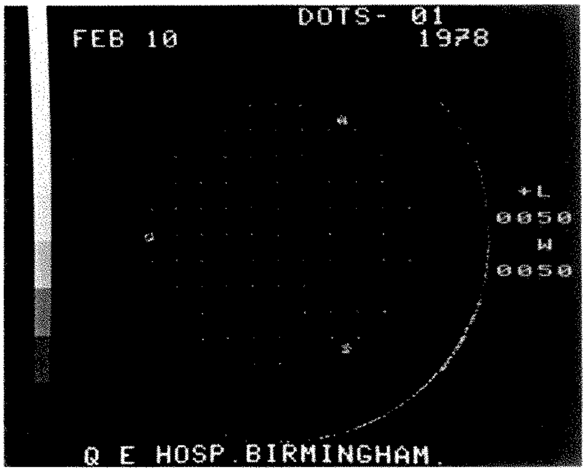

FIG. 3.
Scan of geometric phantom used to establish magnification.

1979, *British Journal of Radiology*, *52*, 832–835

The film was then cut into individual scan transparencies and projected to actual size in a similar way to Munzenrider *et al.* (1977), using a half-plate photographic enlarger. The image of the geometric phantom was used to establish the correct magnification in the region of interest and the image of the scan was then projected onto a sheet of tracing paper on which the patient's outline, obtained by conventional means, had been drawn. Alignment of scan and outline was made simple by means of the surface and couch-top markers. The enlarger, a Lines and Jones half-plate "professional" model fitted with 500 W photoflood bulb, produces an image visible in normal room lighting so that tracing of tumour outlines or other anatomical features is a simple matter. It is intended to modify this arrangement to provide back projection onto the patient's contour for greater convenience of tracing.

Tilted sections

The EMI CT5005 scanner scans in a transverse-axial plane. Although coronal and saggital planes can be constructed from a series of transverse planes this does not provide information in the tilted planes often required for treatment planning.

A tilting couch top has recently been constructed to enable scans of the head and neck to be undertaken with caudo-cranial tilt from 0 to 20 deg. This fastens on top of the flat top previously described (Fig. 1B).

ACKNOWLEDGMENTS

This work was undertaken in the Radiotherapy Physics section under the direction of Dr. A. L. Bradshaw. The couch tops were constructed by Mr. V. T. Woodin and Mr. D. Kerslake of the Radiotherapy Physics Workshop. Photography was done by Mr. T. F. Dee of the Medical Illustration Department, Miss E. Kirkwood of the Department of Diagnostic Radiology produced the illustrated scan. The geometric phantom was lent by Mr. S. H. C. Hughes of the General Physics section and the typing was done by Mrs. P. Doyle. To all these I wish to express my thanks.

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Measurement of ^{57}Co-labelled vitamin B_{12} using a liquid-scintillator whole-body counter

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There is very little information concerning the measurement of ^{57}Co using liquid-scintillator whole-body counters, particularly in relation to its clinical application in measurements of absorption of vitamin B_{12} in humans. In addition to the problem common to all whole-body counters, of scatter and attenuation of the low energy (0.12 MeV) ^{57}Co γ rays within the body, there are other difficulties peculiar to organic scintillator whole-body counters, such as low scintillation efficiency and poor spectral resolution, which limit their use with this radionuclide. Detector signals due to ^{57}Co may be difficult to discriminate from photomultiplier noise and only those counters with high efficiency for light collection are capable of measuring them.

The advantage of using ^{57}Co for this application, instead of ^{58}Co (0.81 MeV), is its lower radiation dose (Rosenblum, 1960). We have therefore investigated the feasibility of measuring the absorption of ^{57}Co-labelled vitamin B_{12} using a liquid-scintillator whole-body counter, whose performance suggested this possibility (Smith, 1976), by comparison with a conventional eight detector NaI whole-body counter.

PATIENTS AND METHODS

Comparative measurements of absorption of vitamin B_{12} were made using both whole-body counters on 40 subjects. One normal male volunteer was included in the group, the remainder being patients presenting with megaloblastic anaemia or undergoing investigation for tropical malabsorption. After fasting overnight, each subject was counted in both counters before, and one hour after, oral administration of a gelatin capsule containing 1.0 μg vitamin B_{12} labelled with 0.5 μCi of ^{57}Co. In addition, two further measurements were made on 16 subjects in order to assess the variation in count rate which occurred during the first hour due to redistribution of administered radioactivity. The times of these extra measurements were somewhat variable but on average were about five and 30 minutes after the dose. In all subjects, absorption was determined by recounting seven to 14 days later and, after correction for radioactive decay, by reference to the 100% value measured one hour after the dose was administered.

The liquid-scintillator (LS) counter was operated in the scanning mode using only four of its eight detectors, as described by Smith and Cronquist (1977), each measurement taking 200 seconds. The choice of ^{57}Co energy window (0.11–0.19 MeV) was largely dictated by the photomultiplier noise spectrum (Fig. 1). The counter background, which was monitored several times during each counting period, was stable during these periods, and any long-term changes, such as those between the day when the patient received the dose and a subsequent day when the absorbed fraction was measured, were allowed for. A small ^{57}Co source was used to monitor counting efficiency at each measurement. The standard error of the method, due to counting statistics alone, was equivalent to about 2% of dose for an absorption of 30% of the administered dose.

Measurements with the NaI counter (Tait and Hesp, 1976) were also made for 200 seconds, using an energy window of 0.06–0.18 MeV. The standard error due to counting statistics for an absorption of 30% of the administered dose was equivalent to about 0.3% of dose. A previous study with this counter showed excellent agreement between absorption values of ^{57}Co-labelled vitamin B_{12}, as measured by whole-body counting and by faecal analysis (Tait and Hesp, 1976). Therefore, no further analysis of faecal radioactivity was considered necessary in the present study. It was sufficient to assess the LS counter performance in such studies by comparison with the NaI counter.

RESULTS

Variations in count rate following oral administration of ^{57}Co vitamin B_{12}

The variations in whole-body count rate during the first hour after oral administration of ^{57}Co-labelled vitamin B_{12} are presented in Table I, expressed as a percentage of the corresponding count rate at one hour. In each counter, mean values at five and 30 min were close to the value at one hour, but there was substantial variation soon after the dose was administered, which diminished with time. Variations observed with the LS counter were less

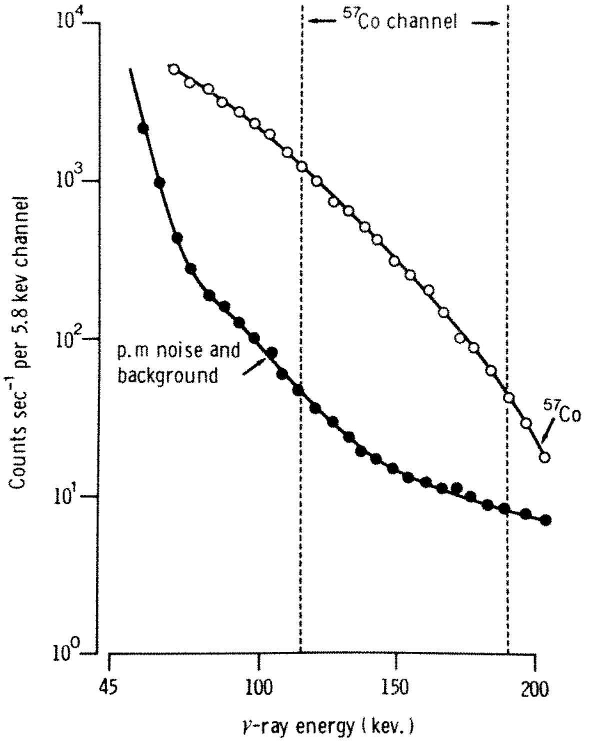

FIG. 1.
Low-energy response from liquid-scintillator whole-body counter.

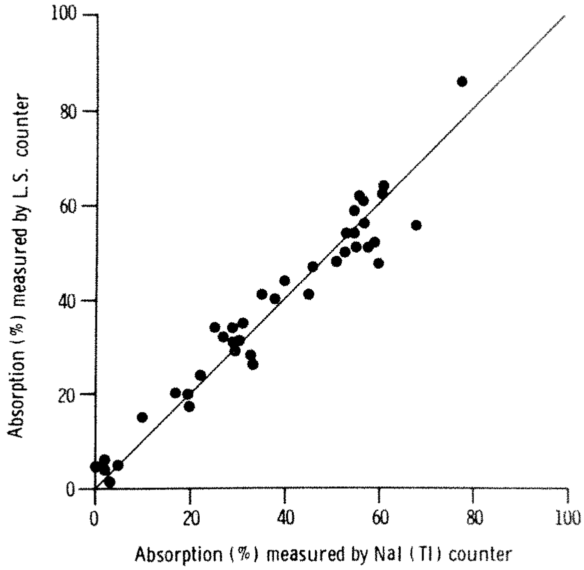

FIG. 2.
Relationship between absorption of ^{57}Co vitamin B_{12} measured with the liquid-scintillator and NaI(TI) whole-body counters. (Line of identity is shown.)

TABLE I

Relative count rates from ^{57}Co in the body at various times after administration (relative count rate at 60 minutes is 100)

	LS Counter		NaI(TI) Counter	
Approximate time, minutes	5	30	5	30
Mean	97.7	97.8	104.2	101.3
Range	84.2–110.7	93.7–103.4	75–135	86–118
S.D.	± 6.8	± 3.1	± 17.3	± 8.7
S.E.M.	± 1.7	± 0.8	± 4.5	± 2.2
n	16	16	15	15

than half those for the NaI counter, with a standard deviation of only ± 3.1% after 30 min.

Comparison of measurements of ^{57}Co vitamin B_{12}

Values of ^{57}Co vitamin B_{12} absorption measured on 40 subjects in both whole-body counters are shown in Fig. 2. These values were all within the range 0–80% of dose, as measured by the NaI counter, of which about two thirds were distributed in the range 30–80% of dose, which has previously been established as the normal range for the NaI counter. The regression of absorption values determined with the LS counter (y%) on those determined with the NaI counter (x%) is given by:

$$y=2.80\ (\pm \mathrm{SE}\ 1.62)+0.934\ (\pm \mathrm{SE}\ 0.038)x$$
$$r=0.970$$
$$n=40$$

SD about regression $= \pm 4.87$% of dose.

The intercept on the y axis was not significantly different from zero ($p > 0.1$) and the slope of the regression line was not significantly different from 1.0 ($p > 0.05$). The correlation coefficient r was highly significant ($p < 0.001$).

The mean difference between 40 pairs of ^{57}Co B_{12} absorption values was not significant (mean 0.17% of dose, SEM ±0.79, $p > 0.1$).

Discussion

Excellent agreement was observed when ^{57}Co B_{12} absorption values obtained with our LS counter were compared with those using a conventional NaI whole-body counter, whose accuracy for this measurement had previously been validated. The mean difference between 40 pairs of measurements, fairly evenly distributed in the absorption range 0–80% of dose, was not significant. The standard deviation of the difference was ± 5% of dose, of which the errors due to counting statistics account for only a small proportion. The residual error (±4.6%) must be due to technical errors of measurement and predominantly to the inaccuracy of the 100% retention values and the differences in radioactivity distribution between retention measurements. If both counters contribute equally to the residual error, each one is subject to an error due to this effect of 3.3% of dose, which is acceptably small to permit reliable measurements of vitamin B_{12} absorption.

The variation in whole-body count rate within the first hour after giving oral ^{57}Co B_{12} was considerably less in the LS counter than in the NaI counter. This is probably due to the use, in the former counter, of a scanning procedure. In both counters, the variation decreased rapidly with time and in the LS counter had reduced to only ±3.1% after 30 minutes. This suggests that the 100% retention with this counter might be measured satisfactorily at 30 minutes after the dose, thereby reducing the patient's waiting time.

The ability of the LS counter to measure ^{57}Co was made possible by the high efficiency for light collection of the detectors and emphasizes the need for careful attention to design. In order to discriminate against photomultiplier noise only a small fraction of the ^{57}Co spectrum could be measured (Fig. 1). Nevertheless, counting efficiency was adequate using 0.5 μCi ^{57}Co, and the counting time of 200 seconds used in this study could be increased if necessary without undue hardship to the patient.

In conclusion, the results of the present study have shown that a whole-body counter based on large liquid-scintillation detectors can be used for the diagnostic measurement of the absorption of ^{57}Co-labelled vitamin B_{12}, provided an efficient scintillator is employed and good light collection achieved. The accuracy is adequate to permit reliable delineation of the normal and abnormal ranges of vitamin B_{12} absorption previously established with the NaI counter.

ACKNOWLEDGMENTS

We wish to acknowledge the technical assistance of Mrs. Christine E. Tait and Miss Margaret McGarry.

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Book reviews

Manuel d'electroradiologie, tome 1. Bases physiques et biologiques. By G. Delorme and J.-P. Tessier, pp. xii + 401, 1978 (Editions Masson, Paris), Fr.190.

This book covers a wide field of subjects, though at varying levels of detail. The principal purpose is stated to be a text for training radiographers and technicians; in addition to radiology there are sections on nuclear medicine, ultrasonics, electrical treatments and diagnosis, thermography and ultraviolet radiation. A chapter on radiation protection is also included. It is a multi-author work which results in some duplication and variable depth of treatment.

Almost half the book is concerned with diagnostic radiology. The technology of image intensifiers and X-ray generators and tubes is given a lengthy discussion; in this respect the book complements an earlier one (traité de radiodiagnostic tome 1, 1969) which was concerned almost entirely with the X-ray beam and the formation of the image.

The sections on diagnostic radiology include recent developments such as tomodensitometry (CAT scanning) and xeroradiography. The other sections are more cursory and sometimes look old-fashioned, for example an illustration of an electron linear accelerator which shows a series of drift tubes of varying length. Radiological SI units are mentioned but not used in the text.

D. K. BEWLEY.

Radiographic Positioning and Related Anatomy. By Isadore Meschan (2nd Edition), pp. vi + 590 illus. 1978 (Holt-Saunders Ltd., Sussex) £14·50.
ISBN 0–7216–6270–6

This is a useful book and should be read by all who are sitting Part 1 of the RCR Fellowship. The layout is clear with concise explanations of the different projections used to demonstrate particular regions; this is helped by line drawings and the use of annotated anatomical diagrams; the labelling on some of the diagrams is however occasionally confusing.

The author has included a useful summary of various radiological procedures in the beginning of the book which is valuable for reference purposes.

The main criticism of the book is in the quality of the CT scans which are poorly defined and will no doubt be changed in the next edition.

J. A. GLEESON.

Radiologic Diagnosis of Polyps and Carcinoma of the Large Bowel. By M. Maruyama, pp. xii + 262, Illus. 1978 (George Thieme Verlag, Germany) DM 186.
ISBN 3–13–5680–01–0

This book, which is concerned with the radiological demonstration of polyps and carcinoma of the colon, is an interesting mixture of magnificent illustrations and poorly written text. This problem could have been avoided by the employment of an English-speaking editor who would have prevented sentences such as:

> "The preparatory steps are most important in such procedure and a well defined picture can be realized after a complete evacuation of the content of the large bowel by sending alternately a small amounts of barium and air from the anus, accompanied by changes in the body position and observation under fluoroscopy" appearing.

The classification and treatment protocol of familial polypoid disease is unusual and is not acceptable in this country.

Unfortunately one cannot recommend this book.

J. J. GLEESON.

Phantom materials for photons and electrons. The Hospital Physicist's Association, Scientific Report Series – 20 pp. 30, 1977, (HPA; London), £2·00.

This booklet has been prepared by the Radiotherapy Topic Group. It provides a brief, well-written account of the various requirements of phantom materials and includes details of substitutes available for fat, muscle and bone in the energy range 0·01 to 50 MeV. The report is a useful reference for those engaged in radiation dosimetry.

Recent advances, such as the application of computerized axial tomography in diagnosis and radiotherapy treatment planning, undoubtedly create the need for greater sophistication in the formulation of adequate phantoms. Readers who are interested in this field are referred to ICRP Publication 23 (Report of the Task Group on Reference Man; Pergamon Press) for an insight into the complexities of the chemical composition of tissues. It is a pity that the ICRP publication is not mentioned in this HPA report since these two sources, taken together, indicate the limitations involved in the formulation of a phantom material as well as providing an admirable introduction to a developing field of study.

A. J. STACEY.

1979, *British Journal of Radiology*, *52*, 836–838

Case reports

False aneurysm of the superior mesenteric artery—a complication of pancreatitis

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Complications and sequelae of pancreatitis are numerous. They vary from simple oedema (phlegmon) to haemorrhagic or infected pseudocysts (abscess) and have a serious prognosis. The gravest outlook for the patient, however, is erosion of blood vessels, usually arteries, by the pancreatic enzymes collected in a pseudocyst. If the "pseudocyst" is not "matured", *i.e.* surrounded by a membrane composed of granulation tissue and later fibrous tissue, spread of the content into neighbouring tissue and organs can be anticipated (Winship, 1977). At this point, lethal haemorrhage can take place. A decision has to be made whether further management should be immediate surgical intervention or conservative medical treatment. The following case illustrates the difficulties. The role of diagnostic ultrasound will be discussed.

Case Report

A 67-year-old male was admitted in August 1978 with a second episode of upper gastrointestinal bleeding. On admission the patient complained of dizziness, weakness and dyspnoea on exertion. He denied epigastric pain. On the previous admission to the same hospital, he had epigastric and back pain and was diagnosed to have: (1) adult onset diabetes mellitus; (2) chronic renal failure secondary to chronic glomerulonephritis; (3) chronic obstructive lung disease; (4) arterial hypertension; (5) anaemia secondary to (a) renal failure and (b) chronic GI bleeding, probably secondary to salicylate treatment, since GI workup was negative at that time and (6) chronic pancreatitis with heavy ethanol intake over a period of years.

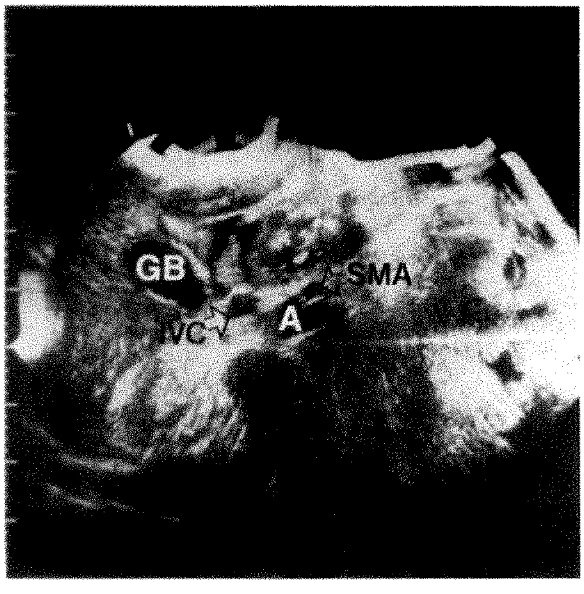

Fig. 1.

Transverse echoscan 8.1 cm below xiphoid. Gall-bladder with thickened wall and an ultrasonic complex mass lesion towards the mid-line and anterior to the great abdominal vessels. Note the sonolucent and strong echo-producing areas within the mass, corresponding to the area of the head of the pancreas (A aorta, SMA superior mesenteric artery, IVC inferior vena cava, L liver, GB gallbladder, M mass)-(3 cm per division).

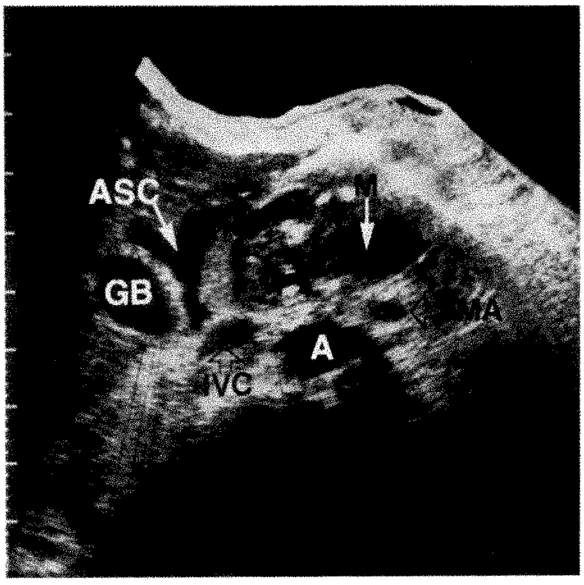

Fig. 2.

Transverse echoscan 5.5 cm below xiphoid. Note free fluid medial to the gall-bladder, the previously seen complex mass, which extends further across the mid-line towards the left and downward displacement of the SMA (2 cm per division).

On this admission, physical examination revealed an emaciated male with normal vital signs. On palpation of the abdomen, the liver was soft and palpable 3 cm below the costal margin (total span=12 cm). The spleen was not palpable and there was no evidence of ascites. Laboratory examination revealed anaemia (Hb=4.7, Hct=15%, MCV=89, MCH=29.4, MCHC=31.5) glucose/blood=127, BUN=66, creatinine=7.1, LDH=360 IU/Lt (normal 95–202), Serum amylase=1300 SU. Gastroduodenoscopy: bleeding lesion in the second portion of the duodenum. Abdominal ultrasonography showed a normal gall-bladder with a slightly thickened wall, a small amount of free fluid in the abdomen, and a mass which was predominantly echogenic, with some internal sonolucent areas, situated in the anatomical area corresponding to the head and body of the pancreas. There was minimal lateral (left) displacement of the superior mesenteric artery in its most proximal portion and slight decrease in AP diameter of the inferior vena cava (extrinsic pressure?). A barium meal showed slight widening of the duodenal loop, but without evidence of ulcer disease. The patient's condition, which was stable for the first three days, became suddenly worse with a further drop in haematocrit and haemoglobin and exploratory laparotomy was performed. A false aneurysm of the superior mesenteric artery was found measuring 5 cm in diameter, approximately 3 cm distal to its origin and extending towards the anterior abdominal wall. The false aneurysm eroded into the duodenum. The patient died the next day.

DISCUSSION

Bleeding into a pancreatic pseudocyst or neighbouring tissue has been frequently described by other authors (Winthrop, 1977; White *et al.*, 1976; Sandblom 1970). Formation of false aneurysms has been also cited (White *et al.*, 1976), *e.g.* in the splenic, common hepatic, transverse pancreatic or coeliac arteries. Winship (1977) described a case of false aneurysm of the superior mesenteric artery, documented by ultrasound and arteriography, but not seen at surgery.

The case presented in this paper was not recognized as a false aneurysm but was described as a haemorrhagic pseudocyst of the pancreas, with clot formation within. This was based predominantly on previous cases where very similar findings were present. Another finding that was present, *i.e.* visualization of the most proximal portion of the superior mesenteric artery, spoke against such diagnosis. Slight lateral displacement of the proximal superior mesenteric artery substantiated also the diagnosis of a pancreatic pseudocyst.

SUMMARY

Early recognition of pseudocyst formation in pancreatitis has been a very important contribution of diagnostic ultrasound. Furthermore, haemorrhage or abscess formation, an additional complication, can also be suspected by this diagnostic modality. False aneurysm formation of a larger, neighbouring

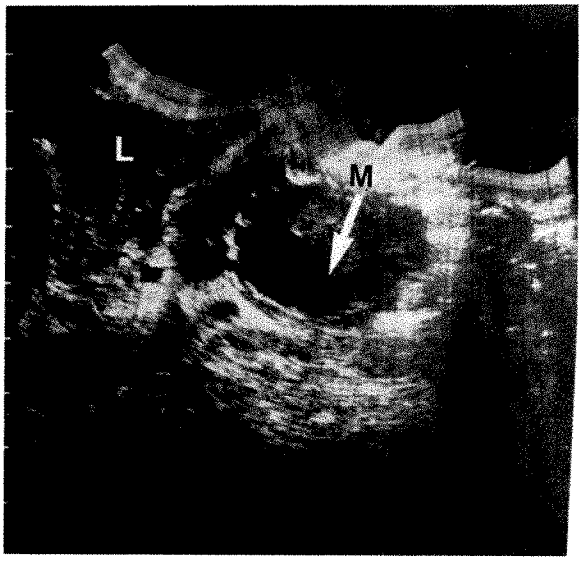

FIG. 3.

Sagittal echoscan 0.5 cm to the left of the mid-line. Large sonolucency with strong echogenic interface craniad and a sonolucent area separating the mass from the liver (duodenum filled with fluid?) (2 cm per division).

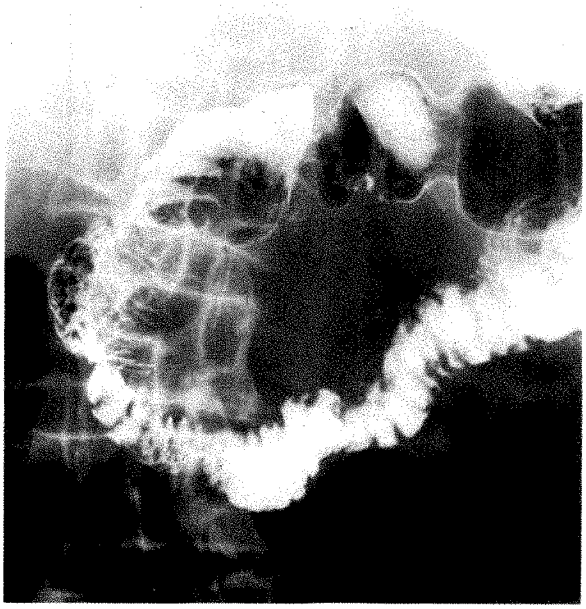

FIG. 4.

Upper gastrointestinal barium meal study. Widening of the duodenal loop, extrinsic pressure (head of pancreas?) with some efacement of the mucosal folds in the second portion of the duodenum.

artery is not easily recognized by ultrasound. It is for this reason that this case report is made.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to Miss Denise Centanni for typing of the manuscript, to Mr. Bernard J. Moore, Jr. and Frederick D. Bailey in the Medical Media Production Service for their excellent illustrations and to Miss Helen Toto of Medical Media Production Service for her artistic contributions in producing this paper.

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Intramural bleeding into a renal allograft pelvis during heparin anticoagulation

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Intramural bleeding into the renal pelvis and ureter has been described in a few patients receiving anticoagulant drug therapy (Antolak and Mellinger, 1969; Buntley and McDuffie, 1976; Garvin, 1979; Kaiser *et al.*, 1975; Smith *et al.*, 1974), in one patient with spontaneous circulating anticoagulants (Eisenberg and Clark, 1976) and in one patient with renal trauma (Kaiser *et al.*, 1975). We report the development of this unusual condition in a renal allograft.

CASE REPORT

A 32-year-old white female with endstage renal failure received a renal allograft from her mother on March 3, 1975. The early post-operative period was complicated by partial ureteral obstruction treated by conversion of ureteroneocystostomy to ureteroureterostomy on the 17th post-operative day. Subsequent complications included a lymphocoele, drained intraperitoneally, and steroid arthropathy of the left knee. Excretory urogram eight months after transplantation showed no ureteral obstruction (Fig. 1).

On December 23, 1977, she was admitted with pain and tenderness in the left groin and swelling of the left lower extremity. The kidney transplant in the left iliac fossa was not tender. Venography confirmed the clinical diagnosis of iliofemoral thrombophlebitis and the patient was placed on intravenous heparin therapy, 150–300 units per hour, which maintained the partial thromboplastin time (PTT) at 50–75 seconds. Three days after the initiation of heparin therapy the patient noticed gross painless haematuria, which persisted intermittently for approximately two weeks. Three urine cultures grew low colony counts of mixed perineal flora. Three urine smears and cultures for acid-fast bacilli were negative, and three cytologic examinations of the urine were negative for malignancy. Urine albumin excretion was unchanged at less than 500 mg per 24 hours. Cystoscopy and voiding cystourethrogram were normal. Excretory urography showed the development of radiolucencies in the wall of the renal pelvis (Fig. 2).

Improvement of the haematuria and the symptoms of phlebitis during the first week of hospitalization was accompanied by a decrease in the number and size of the renal pelvic masses (Fig. 3). After two weeks of heparin

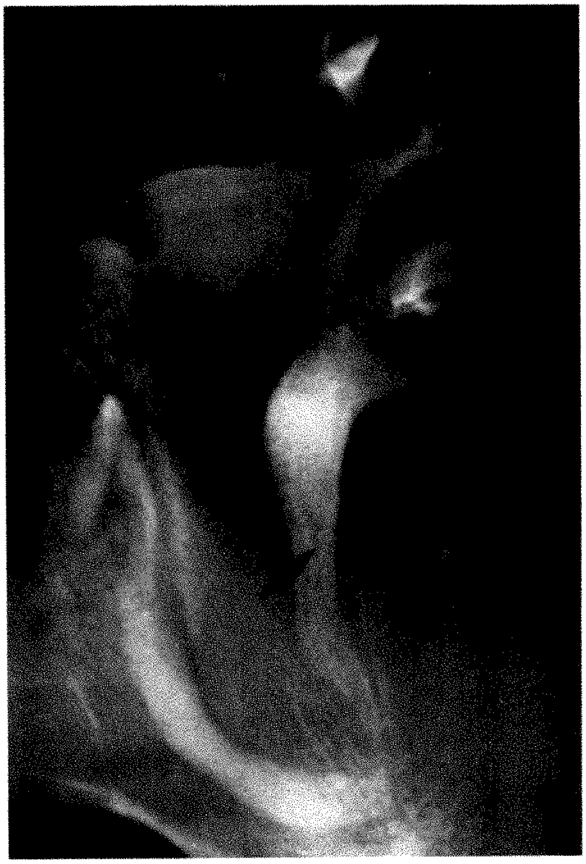

FIG. 1.

Excretory urography eight months after transplantation shows linear striations (arrow) of the renal pelvis and upper ureter. The stirations can be attributed to folds of redundant epithelium resulting from relief by ureteroureterostomy of the earlier ureteral obstruction.

therapy the patient's haematuria resolved, and one week later the urographic appearance had returned to normal (Fig. 4). Coumadin anticoagulation was gradually substituted for heparin.

During the three-week hospitalization the renal function remained stable and unchanged from before the diagnosis of thrombophlebitis: serum creatinine 2.1 mg%, creatinine clearance (uncorrected) 27 ml/min.

Discussion

The most common cause of the urographic appearance of multiple intramural radiolucencies in the renal pelvis and ureter is pyeloureteritis cystica (McNulty, 1957), a chronic inflammatory disease of uncertain and probably varied aetiology. Differentiation of intramural pelvic bleeding from pyeloureteritis cystica depends on the association with anticoagulant therapy or other potential causes of bleeding, the absence of any evidence of infection, and the rapid resolution of the urographic abnormalities. The transient intraluminal mass, consistent with blood clot, provided an additional clue to the correct diagnosis in the present case.

Very occasionally renal vein thrombosis can produce similar urographic appearances (Weiner *et al.*, 1974). Despite the presence of ipsilateral iliofemoral vein thrombosis, we consider renal vein thrombosis excluded by the absence of any changes in albumin excretion, kidney size, or serum creatinine. Severe acute rejection has also produced similar appearances in two of our patients within weeks of transplantation (Stables *et al.*, 1979) but there were no biochemical or clinical features of rejection in the present case.

Linear striations of the renal pelvis and ureter attributable to chronic vesicoureteral reflux or to previous obstruction (Cremin and Stables, 1971) have a different appearance. Indeed, in previous studies of another patient, these striations have been observed associated with a ureteral stricture. Transitional cell carcinoma also produces a different urographic appearance.

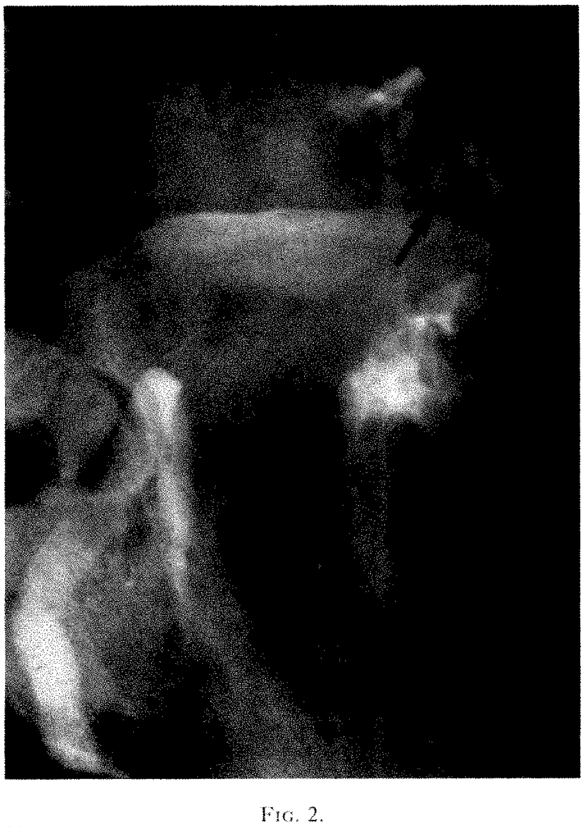

Fig. 2.

Urography two days after the onset of haematuria shows multiple round and oval radiolucencies in the renal pelvis and upper ureter of a character entirely different from the earlier striations and consistent with intramural oedema, haemorrhage, or cysts. An irregular lucency (arrows) in the compound upper calyx has the appearance of an intraluminal mass and is consistent with blood clot.

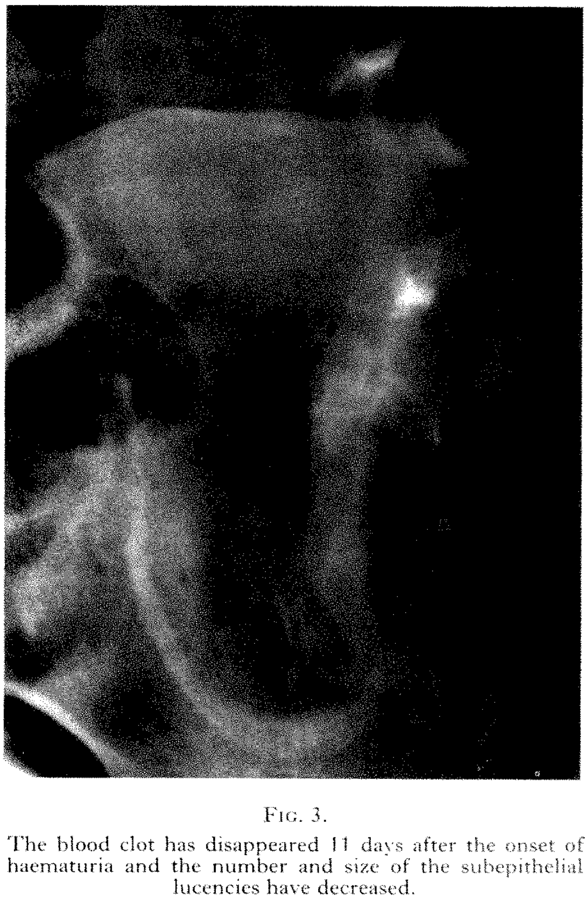

Fig. 3.

The blood clot has disappeared 11 days after the onset of haematuria and the number and size of the subepithelial lucencies have decreased.

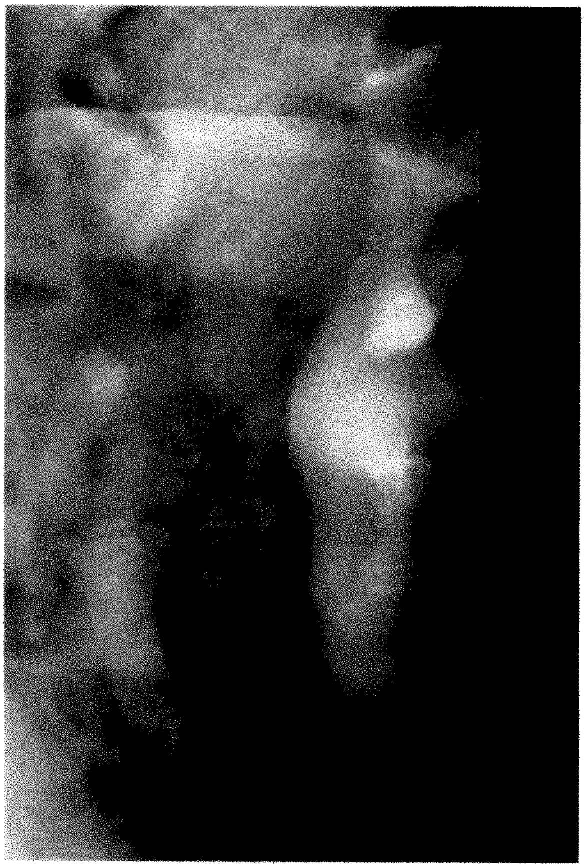

FIG. 4.
Urography 23 days after the onset of haematuria shows return to normal appearance. The previously-observed linear striations are thought to be obscured by the diuresis during this examination.

Recognition of intramural renal pelvic bleeding is important because the condition is self-limited. The present case illustrates that such bleeding can occur in a transplanted kidney during heparin anticoagulation which is within the accepted therapeutic range, and it shows that the haematomas will resolve despite continuation of anticoagulation.

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Haematoma of the wall of the gall-bladder

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(*Received February 1979*)

There are many causes of masses in the right hypochondrium but a search of the English literature has failed to reveal any case resembling the one reported here.

CASE HISTORY

A ten-year-old boy presented with a history of pain mainly in the right side of the abdomen with vomiting of several days' duration. There was a dubious history of very mild abdominal trauma a few days previously but no other previous illness of any relevance. On examination there was a large mass in the right hypochondrium, seemingly attached to the liver but no other abnormality. There was no evidence of jaundice. Liver function tests were normal. An oral cholecystogram (Fig. 1) showed a thin crescentic area of contrast at the lower margin of the soft tissue mass. An intravenous urogram showed compression of the right kidney by the mass but no renal involvement. An ultrasound scan revealed a transonic lesion crossed by at least one strand of soft tissue suggestive of a septum.

At operation a cystic mass was found attached to the under surface of the liver into which ran the cystic artery and cystic duct. This cyst was removed following the ligation of the cystic duct and artery.

Histology of the cyst showed it to contain altered blood and to have a fibrous wall. A structurally normal, compressed gall-bladder was found in the wall of the cyst. The overall appearances were thought to be due to an haematoma of the wall of the gall-bladder.

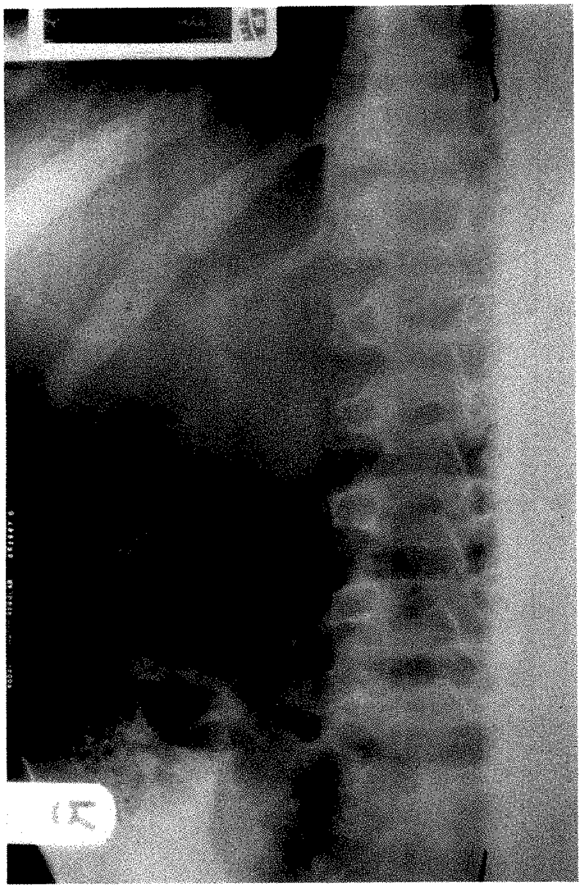

FIG. 1.
Oral cholecystogram showing compressed gall-bladder.

COMMENT

A search of the literature has failed to reveal any case of haematoma of the wall of the gall-bladder. It is possible that our case is a very unusual response to relatively minor trauma as there is no histological evidence to suggest a duplication of the gall-bladder nor was there any evidence of blood dyscrasia, both further clinical possibilities. Evans (1976) reviewed the literature on rupture of the gall-bladder following trauma in children and whilst all the previous cases had biliary peritonitis, in most the interval between trauma and presentation was anything from a few days to six weeks. In some the trauma was relatively minor and there was no evidence of trauma externally as in our case.

The crescentic area of contrast on the oral cholecystogram film presumably represents contrast in the gall-bladder, as it was compressed in the margin of the cystic mass.

ACKNOWLEDGMENT
I should like to thank Professor J. Lister for his permission to report this case.

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Cysticercosis: a report of thoracic disease

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(*Received February 1979*)

INTRODUCTION

Cysticercosis refers to the larval form of infection of Taenia solium, the pork tapeworm. The disease is prevalent in those areas of the world (Mexico, South America, India and China) where raw or inadequately cooked pork is ingested (Manson-Bahr, 1972; Hunter *et al.*, 1966). It results when man serves as the intermediate host of the parasite. Cysticercosis occurs when man ingests viable eggs in food or water contaminated by carriers of the adult pork tapeworm, or by autoinfection in patients harbouring the pork tapeworm.

Each egg releases an embryo or oncosphere which penetrates the blood vessels and lymphatics of the small intestine. The oncospheres are distributed via the mesenteric and systemic circulation, and in two to three months they develop into encysted larvae or cysticerci. The larvae are present mostly in skeletal muscles, subcutaneous tissues, heart, liver, eye and brain (Manson-Bahr, 1972; Hunter *et al.*, 1966, Brailsford, 1941).

A case report of a parietal pleural cysticercal cyst is presented. Review of the radiologic literature failed to reveal a similar example.

CASE HISTORY

A 52-year-old black Haitian woman was admitted for control of diabetes mellitus. Past medical history was noncontributory. Admission chest radiographs (Fig. 1) showed a 2.5 cm smoothly contoured pleural-based lesion adjacent to the third and fourth right lateral ribs. Physical examination was normal, and routine laboratory studies were not helpful.

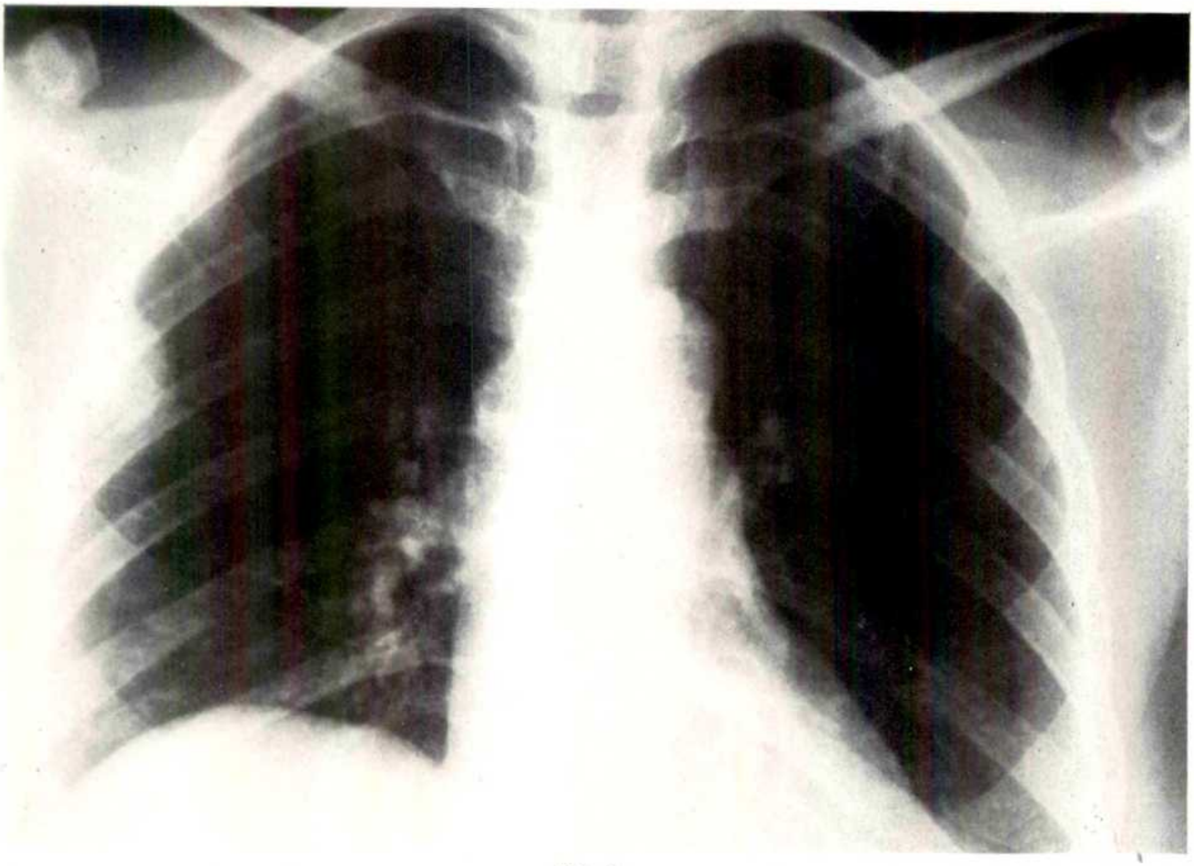
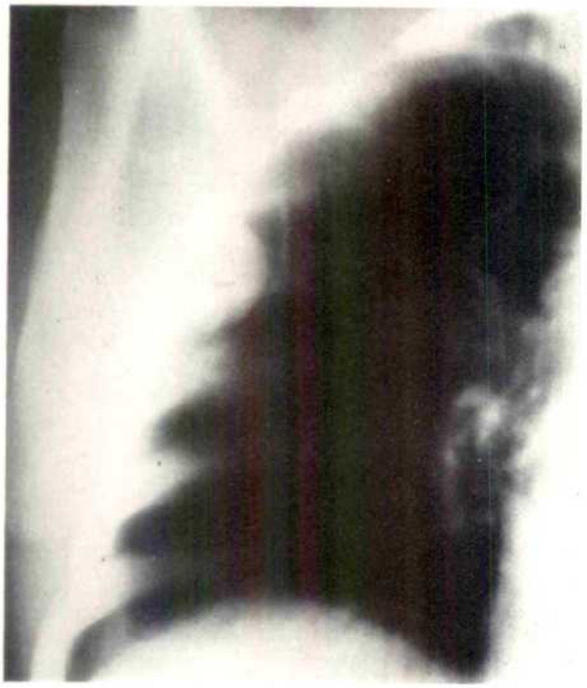


FIG. 1.
Frontal radiograph of the chest reveals a 2.5 cm pleural-based soft tissue density adjacent to the third and fourth right lateral ribs.



Plain film tomography (Fig. 2) showed no calcification within the mass and no rib abnormality. *En bloc* resection of the lesion and the adjacent ribs demonstrated a cyst of the parietal pleura containing a partially necrotic cysticercus larva (Fig. 3). Following surgery, liver scan, computed tomography of the brain, skeletal and extremity radiography failed to reveal other lesions.

DISCUSSION

Our patient presented with a radiographic abnormality with the appearance of a pleural or extrapleural lesion, without bone involvement. The differential diagnosis included soft tissue tumours of the chest wall, inflammation of the chest wall, loculated collections of fluid, pleural thickening, metastasis and mesothelioma. Routine tomography showed no bony abnormality, and excluded lesions arising in bone.

Symptoms caused by cysticerci reflect their location, number and size. Clinical manifestations are

FIG. 2.
Frontal tomogram shows the density to be smoothly contoured. There is no evidence of calcification within the mass. The adjacent ribs appear normal.

most significant when the brain is involved. In other locations, such as skeletal muscle or subcutaneous tissues, symptoms are minimal or absent. Subcutaneous lesions are usually multiple, may be palpable, and can be biopsied.

Initially, there is a local cellular reaction to the parasite, followed by development of a fibrous capsule and cyst. The cyst may range in size from 0.5 cm to 3.0 cm (Hunter *et al.*, 1966). Following death of the parasite, there is degeneration of the cyst and calcification of the parasite. The characteristic calcification is an oval or linear "rice grain" opacity. The size of the calcification is variable, ranging in length from 1 to 23 mm, and is dependent on the size of the cysticercus at the time of its death (Reeder, 1973). The degree of calcification increases with time following the death of the parasite. Five or more years after infection, calcification will be radiographically visible in skeletal muscle in as many as 97% of cases. Intracerebral cysticerci calcify later and less often, and the brain may have radiograpically detectable parasites in only 36% at ten or more years after infection (Manson-Bahr, 1972). Calcification may also occur in the cyst wall, and have a curvilinear appearance (Samuel, 1950).

In a patient from an endemic area, single or multiple soft tissue masses may represent cysticercosis, especially if typical calcification is evident. In such a patient, radiographic evaluation of the skeletal muscles and subcutaneous tissues, especially of the

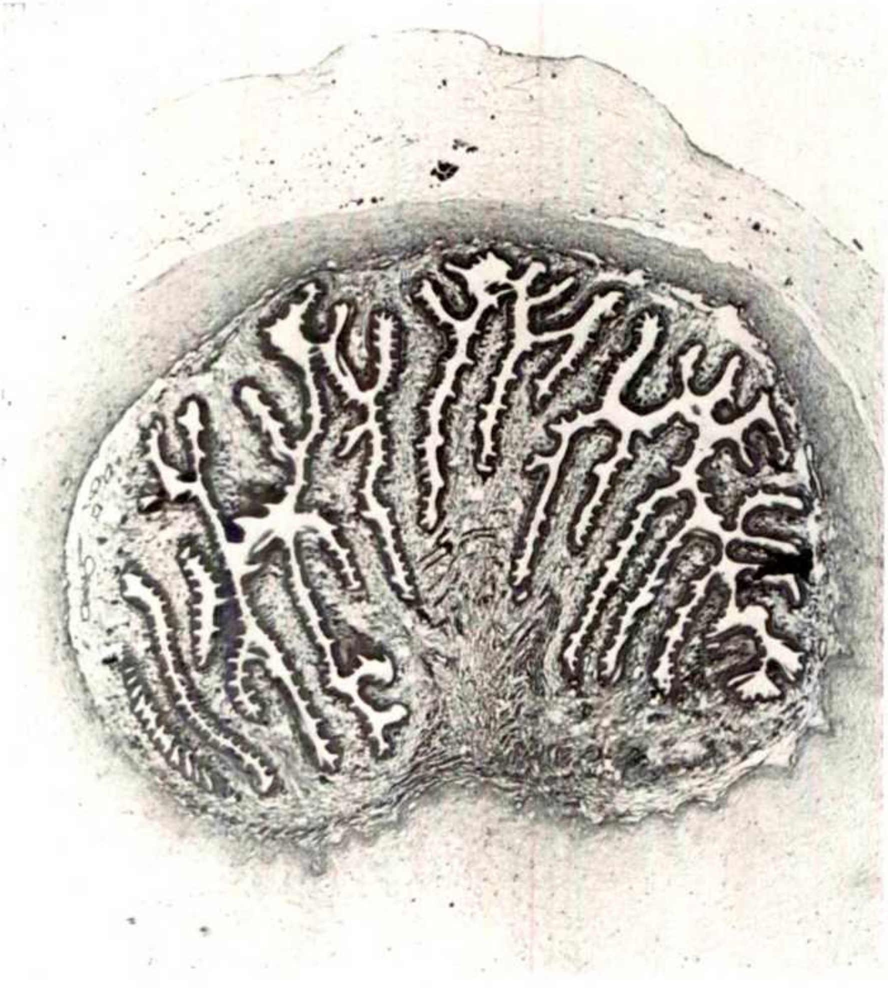


FIG. 3.

Section of cysticercus cyst with dark-staining ectodermal cells (H and E stain at 70× magnification).

lower extremities, and of the brain, should be performed. Computed tomography has proved helpful in the detection of cysticercal cysts in the brain since attenuation differences can be determined and faint calcifications easily detected (Carbajel *et al.*, 1977). Similarly, computed tomography may prove helpful in other areas of the body in the diagnosis of this parasitic disease.

ACKNOWLEDGMENT

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Book reviews

Ultrasonography of Digestive Diseases. By Francis S. Weill, pp. xvi+505, illus., 1978 (C. V. Mosby Co., St. Louis; distributed in UK by Henry Kimpton Publishers, London), £39.

This book reflects Dr. Weill's considerable experience of abdominal sonography. In the preface Dr. Weill admits to some variability in the quality of the grey-scale images, and in part this reflects the numerous real-time illustrations present, which are however, valuable and informative. The book is written in a somewhat breezy style described by the author as "Frenglish" but perhaps more accurately described as "Franglantic". A number of descriptive terms and signs are used by the author, such as the "hail-storm" and "Sieve-pattern" in hepatic metastatic involvement, which are perhaps not in general use. This reflects the need for an international agreement on sonographic terms rather than any criticism of the author's descriptive terms. This an extremely valuable book which contains a wealth of information and fills a place in the ultrasound literature which has previously been somewhat defective. Any department performing abdominal ultrasound would benefit from having this book available.

C H. Wright.

Problèmes de Décroissance Radioactive. By F. Lagoutine pp. 86, 1978 (Commissariat à l'Energie Atomique, France) Fr.60.00.
ISBN 0150-231-X

This monograph is a comprehensive account of the quantitative aspects of radioactive decay. The first section contains a derivation of the basic radioactivity decay equations and discusses half-lives and mean lifetimes of radionuclides. The recommended values of half-lives for over a hundred of the more common radionuclides are listed with their associated uncertainties, most of these values being taken from evaluations of the results of measurements in national and international radionuclide metrology laboratories. There then follows a series of universal decay tables allowing percentage decay with time to be read off for time intervals up to ten half-lives.

The second section is concerned with the growth of radioactivity. The equations for the determination of the activities in individual components in parent-daughter systems are derived and the special cases of transient and secular equilibrium are considered. Four specific examples, ^{49}Ca–^{49}Sc, ^{133m}Xe–^{133}Xe, ^{95}Zr–^{95}Nb and ^{132}Te–^{132}I, are then examined in detail. The general equations for a series of many successive decays are then produced.

The final section contains formulae for the calculation of radionuclide activity during thermal neutron irradiations. The treatment of first order activation with formulae for induced activity, saturation activity and specific activity is followed by the more complicated case of second order activation where a large cross section of the primary induced radionuclide can lead to further neutron capture.

The text is well written with a clear and generally accurate presentation of the many mathematical formulae and graphs, but unfortunately the smallness of print of the numbers in the universal decay tables makes their reading quite difficult. The monograph as a collection of useful formulae in the production, growth and decay of radioactivity may well find wide application in a variety of fields involving the use and measurement of radionuclides.

I. W. Goodier.

Radiology of the Heart and Great Vessels (3rd ed.). By R. N. Cooley and M. H. Schrieber, pp. xiv+673 1978, (Williams & Wilkins Co., Baltimore) $71.50.
ISBN 0-683-02103-6

This book is directed at the radiology resident in training and the general practitioner in diagnostic radiology. It aims to provide the sufficient clinical and physiological background to enable the resident in radiology to participate in combined teaching sessions and the activities of the cardiac catheterization laboratory.

The writing is cumbersome in the extreme and the text contains long descriptions of the contents of references (the flow rates of Taussig and Big's original case are given!). The quality of the illustrations is very variable. Although great weight is given to oblique plain films, the oblique angiocardiogram is largely ignored. Many angiocardiograms are non-selective and a number are of poor quality. In spite of these criticisms the book does cover most conditions and while some of the radiological descriptions are rather inadequate, the basic anatomy and physiology are usually quite well done. In general it does fulfil its purpose.

M. J. Raphael.

1977, *British Journal of Radiology*, 50, 845–846 OCTOBER 1979

Short communications

Neoplastic transformation following split doses of X rays

By Carmia Borek, PhD.

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(*Received November 1978 and in revised form March 1979*)

Most data for radiation-induced malignancies in the human relate to a large single dose of radiation received in an acute exposure. An interpolation is required in order to arrive at cancer risk estimates for low doses or low dose-rates which are relevant to human medical or environmental exposure (Brown, 1977; Upton, 1977). Both the BEIR (BEIR, 1972) and UNSCEAR (UNSCEAR, 1977) committees have used a linear interpolation from high to low doses, which assumes that the risk per rad is independent of dose or dose-rate. Risk estimates calculated in this way are assumed to be "conservative", since it has been reported that the biological consequences of a given dose are reduced when that dose is divided into a number of fractions and delivered over a prolonged period of time (Hornsey and Silini, 1962; Elkind and Whitmore, 1967; Belli *et al.*, 1967). Our experiments indicate that this is not always true in the case of neoplastic transformations produced *in vitro*.

The experiments involved fresh explants of diploid hamster embryo cells. The details of the methodology have been published previously (Borek and Sachs, 1966; Borek and Hall, 1973, 1974; Borek *et al.*, 1978). Briefly, cells derived from freshly dissociated mid-term hamster embryos were seeded at low density to allow for clone formation. Following overnight attachment, cells were irradiated with 210 kV X rays, either in a single exposure or in two equal fractions separated by five hours. Cultures were incubated at 37°C for nine to ten days before being fixed and stained. Transformed clones were readily identified by their appearance, since they consist of piled-up cells, randomly arranged. The relationship between the morphological appearance of these clones and their tumourigenicity has been amply documented (Borek and Sachs, 1966; Borek and Hall, 1973, 1974; Borek *et al.*, 1978).

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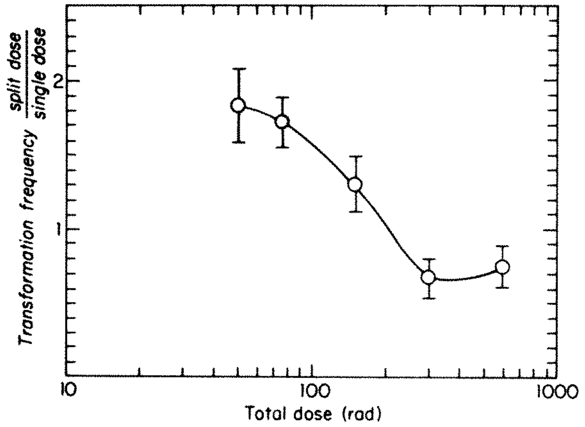

FIG. 1.

Dose response relationship for cell transformation following split and single doses of X rays.

Doses between 150 and 600 rad were used, delivered as single or split exposures. The transformation frequencies obtained are summarized in Table I and plotted in Fig. 1; included are our earlier data for the low-dose range of 50 and 75 rad (Borek and Hall, 1974). In Fig. 1, the quantity plotted on the ordinate is the ratio of the transformation frequencies relating to split versus single doses. For the three lower doses, this ratio is clearly in excess of unity indicating that split doses produce more transformation than a single exposure to the same total dose. At the higher doses the opposite is true; fractionation leads to a reduction in the transformation frequency.

There have been several previous reports in the literature concerning the effect of split doses on *in vitro* transformation. Using fresh explants of diploid hamster cells, Borek and Hall (1974) demonstrated that an X-ray dose of either 50 or 75 rad, split into two equal fractions, increased the transformation frequency by more than 70% compared with the same total dose given in a single exposure. Using higher doses and a heteroploid established mouse cell line (10T½), Little and Terzaghi (1976) reported a decreased transformation frequency following dose fractionation. More recently Miller and Hall (1978), employing the same mouse 10T½ cell line, confirmed the results of both previous reports. Because of the relevance of this area of research to the estimate of human cancer risks due to the accumulation of multiple small increments of radiation dose, the present series of experiments was designed to investigate the effect of fractionation over a wide range of doses using fresh explants of diploid cells.

The evidence provided by our cellular studies with fresh explants of diploid cells is relevant to the problem of cancer risk estimates in the human. Since splitting a dose of 50–150 rad into two equal fractions separated by an interval of five hours can enhance the frequency of transformation, the use of a linear interpolation from high to low dose levels may lead to risk estimates that are neither conservative nor prudent, depending on the distribution of the dose in time.

ACKNOWLEDGMENTS

Thanks to Dr. E. J. Hall for helpful discussion and to Miss C. Pain and Mr. H. Mason for skilful technical assistance.

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Short Communications

TABLE I

NEOPLASTIC TRANSFORMATION OF HAMSTER EMBRYO CELLS FOLLOWING SINGLE AND SPLIT DOSE OF X RAYS

Dose (rad)	Total No. clones counted	Number of experiments	Mean survival fraction*	Total transformed clones counted	Mean % cell transformation† ±1 standard error	Split dose/single dose ±1 standard error
Control	51,699	4	1.0	0	0	0
25+25	15,582	4	0.96	55	0.35±0.05	1.84±0.24
50	14,272	4	0.92	27	0.19±0.04	
37.5+37.5	23,762	5	0.92	255	1.07±0.07	1.72±0.17
75	25,882	5	0.89	160	0.62±0.05	
75+75	13.118	3	0.73	110	0.83±0.08	1.30±0.18
150	15,348	3	0.65	98	0.64±0.06	
150+150	11,925	3	0.58	48	0.40±0.06	0.67±0.13
300	11,450	3	0.47	69	0.60±0.07	
300+300	11,037	3	0.15	48	0.43±0.06	0.74±0.14
600	11,818	3	0.10	69	0.58±0.07	

$$\text{*Survival fraction} = \frac{\text{Number of surviving clones counted}}{\text{Number of cells seeded} \times \text{plating efficiency}}$$

$$\text{Plating efficiency} = \frac{\text{Number of clones counted in control plates}}{\text{Number of cells seeded in control plates}}$$

$$\text{†Cell transformation (\%)} = \frac{\text{Number of transformed clones}}{\text{Number of clones counted}} \times 100$$

transformation of single cells. *Nature*, *252*, 499–501.

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Biliary and faecal excretion of misonidazole in man

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(Received February 1979 and in revised form April 1979)

Although the radiosensitizer misonidazole is now being used widely in clinical trials, much more information is required concerning its metabolism and routes of excretion. This information will be useful in optimizing ways of using the drug in order to reduce peripheral neuropathy, which is its main dose-limiting toxicity, and in the design and development of new drugs structurally related to misonidazole.

Flockhart *et al.* (1978) have investigated urinary excretion in man and shown that only 10–20% of the administered dose of misonidazole is excreted in the urine in the first 24 hours as unchanged drug, plus its o-demethylated metabolite (Ro-05 9963). Less than 1% is excreted as misonidazole glucuronide, while a study using ^{14}C labelling showed that only 2% is excreted as amine derivative. By 48 hours the ^{14}C study showed that nearly 50% of the drug can be identified and accounted for and that a further 29% of the label is excreted in the urine as unidentified substances. They suggested that incomplete absorption of the drug, biliary excretion or direct secretion into the gut could account for the remaining unidentified drug.

We have studied the excretion of misonidazole in the bile and in faeces, as well as in the urine of patients receiving the drug. The results of urinary excretion studies are similar to those of Flockhart *et al* (1978) and show that in the first 24 hours 10–17% of the drug is excreted as misonidazole plus desmethyl misonidazole (Table I).

Biliary excretion of misonidazole was studied in two patients who had undergone surgery for gall-stones and had T-tubes draining the common bile duct. Each was given 1 g misonidazole by mouth and samples of bile and blood were taken at regular intervals. Both patients gave informed consent.

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TABLE I

24 HOUR URINARY EXCRETION OF MISONIDAZOLE AND DESMETHYL MISONIDAZOLE (RO–05 9963) AFTER A SINGLE ORAL DOSE

Misonidazole dose, g	Excreted as misonidazole, %	Excreted as desmethyl–m, %	Total excreted as per cent of oral dose
5	4.04	7.78	11.82
6	5.5	6.4	11.90
4	6.94	9.84	16.78
5	6.3	5.3	11.60
2	4.4	5.8	10.2

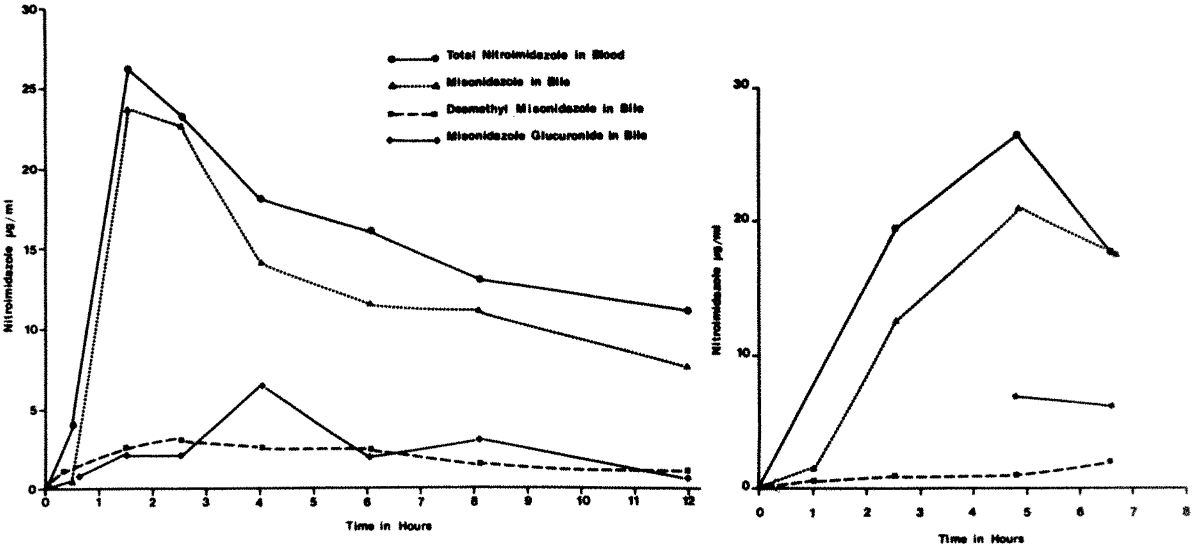

FIG. 1.

Case 1. Bile flow rate 30 ml/hr

Case 2. Bile flow rate 8 ml/hr

Excretion of misonidazole, desmethyl misonidazole (Ro–05 9963) and misonidazole glucuronide in bile in two patients.

The concentration of misonidazole and desmethyl misonidazole was measured by high pressure liquid chromatography (HPLC) according to the method of Workman *et al.* (1978) and misonidazole glucuronide in bile was also measured by HPLC after overnight incubation of the specimen with β glucuronidase (Glucurase, Sigma). The results are shown in Fig. 1. The concentration/time graphs show that the misonidazole level in bile parallels that in blood and suggests that passive free diffusion may be the mechanism of drug entry into the bile. Calculation of the total drug excreted into the bile in 12 hours in case one shows that 0.9% of the administered dose of the drug is excreted into the common bile duct as unchanged drug and that desmethyl misonidazole and misonidazole glucuronide comprise only 0.16 and 0.13% of the oral dose. Case two in which there was a much lower flow-rate of bile and in which jaundice was still present, showed an excretion of less than 0.1% of the drug into the bile in six hours.

Faecal excretion was investigated in two patients, one after a single oral dose of 5 g misonidazole and the other in the second week of daily treatment at a dose of 0.4 g/day. No unchanged drug or desmethyl misonidazole was detected in the faeces in either case.

Neither the data of Flockhart *et al.* (1978) nor our own have fully identified the metabolism and routes of excretion of misonidazole. The studies show that little of the drug is excreted in unchanged form and that there is little metabolism in the form of o-demethylation, glucuronidation or amine formation. Measurements on urinary and faecal excretion have not identified more than 50% of the drug excreted in the first 48 hours and the measurements of bile show that very little drug is excreted by this route.

Incomplete absorption of the drug from the gut cannot explain the deficit since blood levels of misonidazole are consistent with complete absorption and free distribution throughout the body fluid (*i.e.* 1 g distributed in 50 l body fluid would produce a level of 20 μg per ml which is roughly the level usually obtained).

Active secretion of the drug into the gut may occur but it is more likely that it passes into the gut by passive free diffusion and is then broken down by anaerobic bacteria so that none is identified in the faeces. This is likely, however, to be a negligible route of elimination.

A probable explanation for the failure to identify all the metabolites and routes of excretion of the drug is that it is broken down to short-lived highly reactive and water-soluble compounds that cannot yet be identified. Investigation of these products, however, may be necessary in order to improve the therapeutic efficiency of this promising drug.

ACKNOWLEDGMENT

Misonidazole was supplied by Roche Products Limited, Welwyn Garden City, Herts.

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Book reviews

Traité de Radiodiagnostic. Vol. VIII. Appareils urinaire et génital masculin. Surrénales. By G. lemaitre, J. R. Michel and J. Tavernier, pp. XVIII +622 illus., 1978 (Masson et Cie) 550 F.
ISBN 2-225-71401-0

This book is the second edition of the 8th volume of the French textbook: *Traité de Radiodiagnostic*, divided into 20 volumes. The work has some 60 authors, mainly French radiologists of renowned competence in the field.

The volume reviewed here has been composed under the supervision of G. Lemaitre, J. R. Michel and J. Tavernier.

Compared with the previous edition, some chapters are completely new, *e.g.* the radiology of renal insufficiency and the radiology of subcapsular, perirenal and pararenal collections. Recent developments in the field of radioanatomy and renal physiopathology are here remarkably well integrated.

Other chapters have been completely revised and rewritten: *e.g.* renovascular hypertension, renal cysts, adrenal glands, mycotic infections and the problems of kidney transplantation, and they reflect the most recent knowledge in this field.

As in the first edition this book is very handsomely printed with a minimum of typographical errors and the quality of the illustrations is excellent. What is more, most of the illustrations have been changed since the first edition.

New radiological techniques, namely echotomography and computer tomography have not been forgotten. However, the chapter on CT is rather superficial; only four lines are devoted to the CT of the adrenal glands; sinus lipomatosis is not described. Moreover the quality of the CT images is also out-of-date compared with the fast new generation scanners. This is of course a consequence of the rapid technological evolution in this field.

These minor criticisms are not intended to detract from the value of this book, which is strikingly-homogeneous in spite of the 13 co-authors.

We can therefore recommend this book without hesitation. The purchase of it is, despite the rather high price, justified because of the up-to-date content, the well written text and the excellent illustrations.

A. BAERT.

Clinical Ultrasound of the Breast. By Toshiji Kobayashi, pp. xv+174, 67 illus., 12 tables, 1978 (Pitman Publishing Ltd., London, Plenum Publishing Corporation, New York), £16·00.
ISBN 0-272-79514-3

The use of ultrasound in the investigation of breast disease has been developed and assessed in Japan for over 20 years. Dr. Kobayashi has been associated with this work and has a wide experience of the technique.

The book is mainly set out as an atlas as the author believes that demonstration rather than description is the best method of imparting information. In spite of this there are precise and adequate descriptions of the characteristics of the various lesions demonstrated.

There is an introductory chapter in which the history of breast echography is tabulated and the method of examination briefly described. The diagnostic criteria suggested by various authors and the dependability of the various signs are also tabulated. It is interesting to note in the comparison of the diagnostic accuracy rates of ultrasound and mammography that not in one instance is mammography superior to ultrasound. This may well be a reflection of the difficulties of achieving good mammography of the Oriental breast, a fact which possibly led to the Japanese interest and development of breast echography.

The remainder of the book is the annotated atlas and is divided into three parts. part 1, the largest section, deals with bistable echography using the sensitivity-graded method to distinguish the various features of benign and malignant lesions, part 2 illustrates grey-scale imaging and part 3, expanded echography. This latter technique involves electronic magnification of the lesion. The resulting echogram shows more detail and is considered to be more effective in the diagnosis of early breast cancer.

Diagnostic signs of benign and malignant lesions are well described and abundantly illustrated. The quality of the images and reproductions is excellent. The bibliography is comprehensive and up to date.

This atlas makes an important contribution to the subject of breast imaging and at present is the only book devoted entirely to breast echography. It illustrates the diagnostic possibilities of this non-invasive method and should be of interest to all involved in the management of breast disease.

I. H. GRAVELLE.

Roentgenologic Anatomy of the Lung. By H. Yamashita, pp. vii+389, 1978 (Georg Thieme Verlag). D M 248.
ISBN 3-13-5681-01-7

The purpose of this book is "to represent a thorough study of the topography of the pulmonary segments including structures and the ramifications of the bronchi and blood vessels".

It is beautifully produced, lavishly illustrated and expensive. The book extends over nearly 400 pages giving an extremely detailed account of bronchopulmonary anatomy. The anatomical descriptions are based on a careful analysis of many cadaver lungs. The book represents a painstaking account of normal anatomy with its variations and there can be few, if any, texts which offer such detailed anatomy. Indeed, it is such a *tour de force* that many readers may be overwhelmed by the quantity of information. A highly complicated terminology for segmental and subsegmental bronchi and vessels together with an occasionally indifferent English translation renders the whole somewhat undigestible.

I very much doubt whether any general radiology department will find this book very useful. For dedicated pulmonary radiologists it will be a very useful reference book–if they can afford it.

C. D. R. FLOWER.

Correspondence

Running of ultrasound departments

THE EDITOR—SIR,

Having developed a particular interest in ultrasonics over the past six years and in consequence appreciating the value of this branch of the imaging field and hopefully having some little insight into the future of this rapidly developing science I am rather unhappy regarding the running of some ultrasonic departments.

I feel that there are too many departments where there is no radiologist actively participating or where he is merely a figure-head and where the ultrasonic technician is for all practical purposes working in a void. At best she may be working full-time in the ultrasonic department but even worse she may be doing only one or two sessions per week, the rest of the time being spent in the X-ray department. I feel very strongly that a radiologist should be actively involved and that the ultrasonic technician should be full-time. Only if these fundamental requirements are met will the department provide the best possible service and be used to best advantage by the clinicians. It must be remembered that ultrasonics is still something of a mystery to many clinicians and they certainly need guidance in using the facilities. An ultrasonic technician who has the help and support of an actively involved radiologist will obviously be much happier in her work and will have the opportunity to develop and expand her techniques whereas if she is working alone she is in danger of being flooded by unnecessary requests, to the detriment of the mother-to-be in particular.

May I make a plea that even if the radiologist in a department does not have a particular interest in ultrasonics he makes sure that his technician receives the best training possible and thereafter gives her his support and, if necessary, "medical weight".

In the not too distant future it is to be hoped that the radiological staffing situation will be such that an adequate number of radiologists are able to devote themselves mainly or even wholly to this fascinating and extremely valuable branch of the art.

Yours, etc.,
R. D. WOOD.

Ultrasonics Department,
Hope Hospital,
Eccles Old Road,
Salford 6,
Lancs.

(*Received May 1979*)

Radiation protection syringe housing

THE EDITOR—SIR,

When technetium 99m is injected into a patient prior to a radiosiotope scan of brain, liver, bone, etc., the radiation protection procedure adopted to limit the dose to the clinician's fingers involves the use of a shield surrounding the radioactive syringe. There are a variety of such shields in use, but the basic design is usually a cylindrical lead holder containing a lead glass insert for viewing the syringe scale. Exceptions are the shields manufactured by Nuclear Pacific, Inc., of Seattle, which are constructed totally of lead glass. In practice, though, individual syringe shields are cumbersome to use; to overcome this problem a special type of syringe housing was made at Westminster Hospital some four years ago. Since that time, it has been in routine use and has proved to be very satisfactory. The syringe housing (Fig. 1) consists of a solid lead base clad in polished stainless steel, recessed to hold three syringes of capacity 10 ml, 5 ml and 2 ml, and a hinged top-plate containing three lead glass (4.2 g Pb/cm^3) viewing windows. These are each of 12 mm thickness and represent 3.3 mm lead equivalent at 150 keV. The remainder of the top-plate surrounding the lead glass windows is fabricated using lead (12 mm) and thus provides more than adequate protection. When a syringe is in position the top-plate is locked to the base and the injection is carried out using a butterfly needle. The catheter is flushed using the patient's blood to avoid retention of technetium 99m within the catheter. This system avoids the disadvantage of using a heavy individual syringe shield, but still retains the necessary radiation protection features.

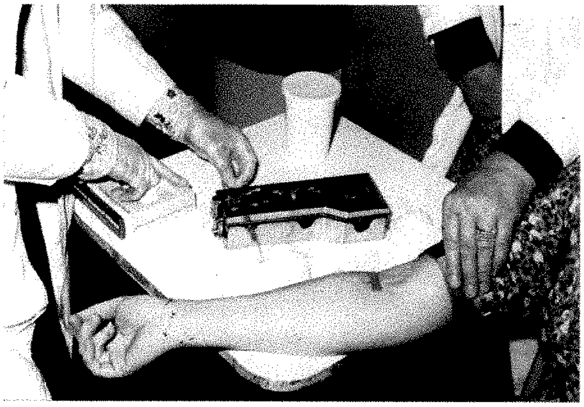

FIG. 1.
Syringe housing for ^{99}Tc^{m} shown in use.

Yours, etc.,
M. J. GRAY, P. BALDWIN,
A. OVERILL, G. DEACON,
R. F. MOULD, J. P. NICHOLSON.

Physics Department,
Westminster Hospital,
Page Street Wing,
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(*Received February 1979, revised June 1979*)

Erratum

It has been noted that in the Letter to the Editor published in *The British Journal of Radiology*, *52*, February 1979 on page 158 in Table I, final column, the dates should read 1944–1962.

We apologise for this error.

Forthcoming events

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of the penultimate month preceding publication (*i.e.* April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Non-obstetric Real-time Ultrasound

An evening meeting, organized by The British Institute of Radiology, to be held on October 18, 1979.

Further details from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

Nuclear Medicine Versus The Rest

To be held on November 14, 1979, this meeting is to review the present contribution of nuclear medicine to the investigations and diagnosis of disease in the context of competing techniques. It is hoped to define the limitations of particular applications and indicate areas for potential growth. There will be three sessions including review papers covering applications in: 1. lungs and cardiovascular system; 2. GI tract and urinary system and 3. skeletal and other systems.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

Paediatric Radiology

A two-day course in diagnostic paediatric imaging will be held at the Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London WC1 on November 15–16, 1979. The main theme of this course will be the respiratory/cardiovascular system.

Further details and application forms are available from The Secretary, Department of Paediatric Radiology, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Radiobiology Meetings

The three work-in-progress meetings this year 1979/80 will be "The role of the stroma in radiation responses" on November 16, 1979, a general meeting on February 15, 1980 and "Biological effects of doses below 2 Gray" on May 19, 1980. Also, there will be an all-day meeting, with invited speakers on Saturday, December 8, 1979, "The rationale for unorthodox fractionation". All meetings will be held in the Institute's Reid-Knox Hall. Titles and preliminary abstracts of proffered papers for the November meeting should reach Dr. J. H. Hendry, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Withington, Manchester M20 9BX, by October 8, 1979.

The British Medical Ultrasound Society
11th Annual Scientific Meeting

To be held on December 17–18, 1979 in Edinburgh.

Authors wishing to submit contributions for consideration should send the title and 100–200 word abstract to the address below before September 15, 1979. Additional background information on the work would help in planning the programme.

Address for enquiries: Dr. W. N. McDicken, Department of Medical Physics and Medical Engineering, The Royal Infirmary, Edinburgh EH3 9YW.

International Course on Bone Scintigraphy

Will take place on January 24–25, 1980 at the Medical Faculty of the University of Leiden, The Netherlands.

For further information contact: Boerhaave Committee for Post-Graduate Education, University Hospital Leiden, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands and mention Boerhaave Course Bone Scintigraphy; or contact: Dr. E. K. J. Pauwels, Dept. of Diagnostic Radiology, Division of Nuclear Medicine, University Hospital Leiden, Rijnsburgerewg 10, 2333 AA Leiden, The Netherlands.

Modern Gastrointestinal Radiologic
Modern Gastrointestinal Radiologic Techniques for the Practising Physician

San Francisco, January 26–27, 1980.

For further information contact: Radiology Postgraduate Education Section Room M396, University of California, San Francisco, California 94143 or call (415) 666–5731.

Computed Tomography in Oncology

ESCAT 2, European Seminar on Computed Tomography in Oncology, will be held at the Excelsior Hotel, London, Heathrow from February 4–7, 1980.

The meeting will be of interest to radiologists, physicists, radiotherapists and members of related disciplines and there will be invited speakers from Europe and the USA, together with a limited number of proffered papers.

Topics include primary diagnosis; staging; therapeutic response; radiotherapy treating planning; tissue characterization.

Further information from: Dr. Janet Husband, Organizing Secretary, The Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT.

5th International Congress of the International Radiation Protection Association

Will take place in Jerusalem, Israel, March 9–14, 1980.

The scientific programme of the Congress will cover all aspects of radiation protection with emphasis on its central theme: radiation protection—a systematic approach to safety.

An interesting programme has been planned including a commercial exhibition and pre- or post-congress workshops and professional tours.

Social events and a programme for accompanying persons have been organized.

For further information: The Secretariat, 5th International Congress of IRPA., PO Box 16271, Tel Aviv, Israel.

B.I.R. Annual Congress 1980

The British Institute of Radiology Annual Congress will be held on April 17–18, 1980 and will include the Sylvanus Thompson Memorial Lecture, presented by Sir Richard Doll.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

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Subscription rates
We would draw attention to an omission to update the USA subscription rate in the inside front cover of the September issue. This should read $103.

Guidelines for the Preparation of Radiopharmaceuticals in Hospitals
Revised 1979 Edition
Special Report No. 11
A Report of a Working Party

Numerous types of diagnostic agents labelled with radio-nuclides are now in routine use for the investigation *in vivo* of human disease. Many of these radiodiagnostic agents contain radio-nuclides of short half-life and for this and other reasons it is necessary to carry out their preparation in hospitals. Little official or other guidance concerning the basic procedures required for the safe preparation of these radiopharmaceuticals has, however, been available. For this reason, following a Seminar on 'Laboratory Facilities and Working Procedures for the Hospital Preparation of Radiopharmaceuticals' held at the Royal Marsden Hospital, Sutton, in October 1974, a working party was set up to prepare some guidelines on this subject. This document comprises the report of this working party; it is concerned not with individual recipes, but with basic principles and procedures. The Report should prove helpful to many of those concerned with the preparation and use of radiopharamceuticals, and it is expected to provoke useful comment and discussion, especially on the extent to which the procedures set down conform to the requirements of the Medicines Act (1968).

In revising the present report it has not been considered necessary to revise any of the original recommendations. However, the opportunity has been taken to amend certain sections to take account of the changes in United Kingdom legislation consequent on the implementation of Article 5(a) of the European Communities Directive (Euratom, 1976) on basic safety standards for health protection against the dangers of ionizing radiation.

Additional references have also been provided, and minor changes made, where necessary to bring the text up-to-date.

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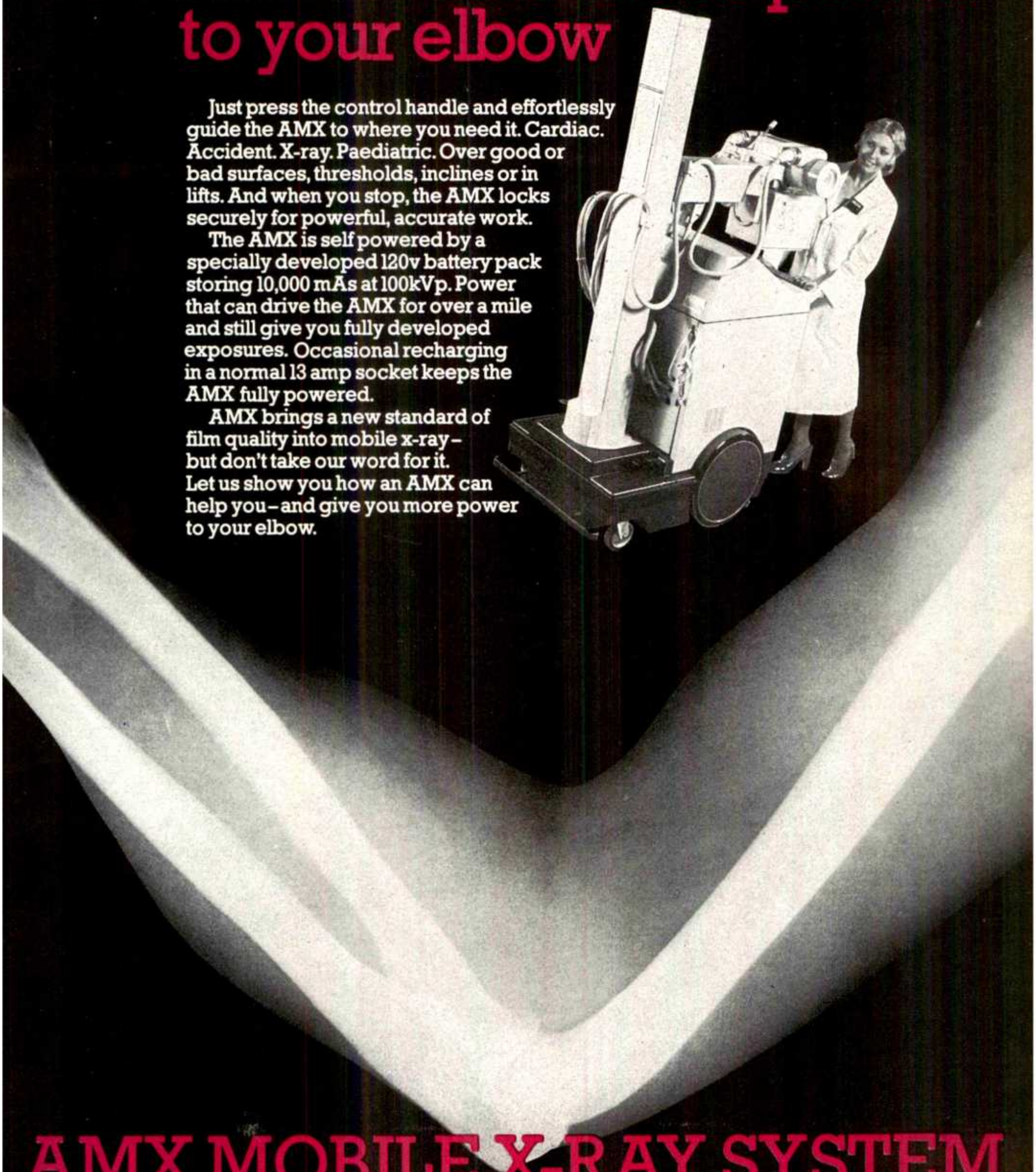

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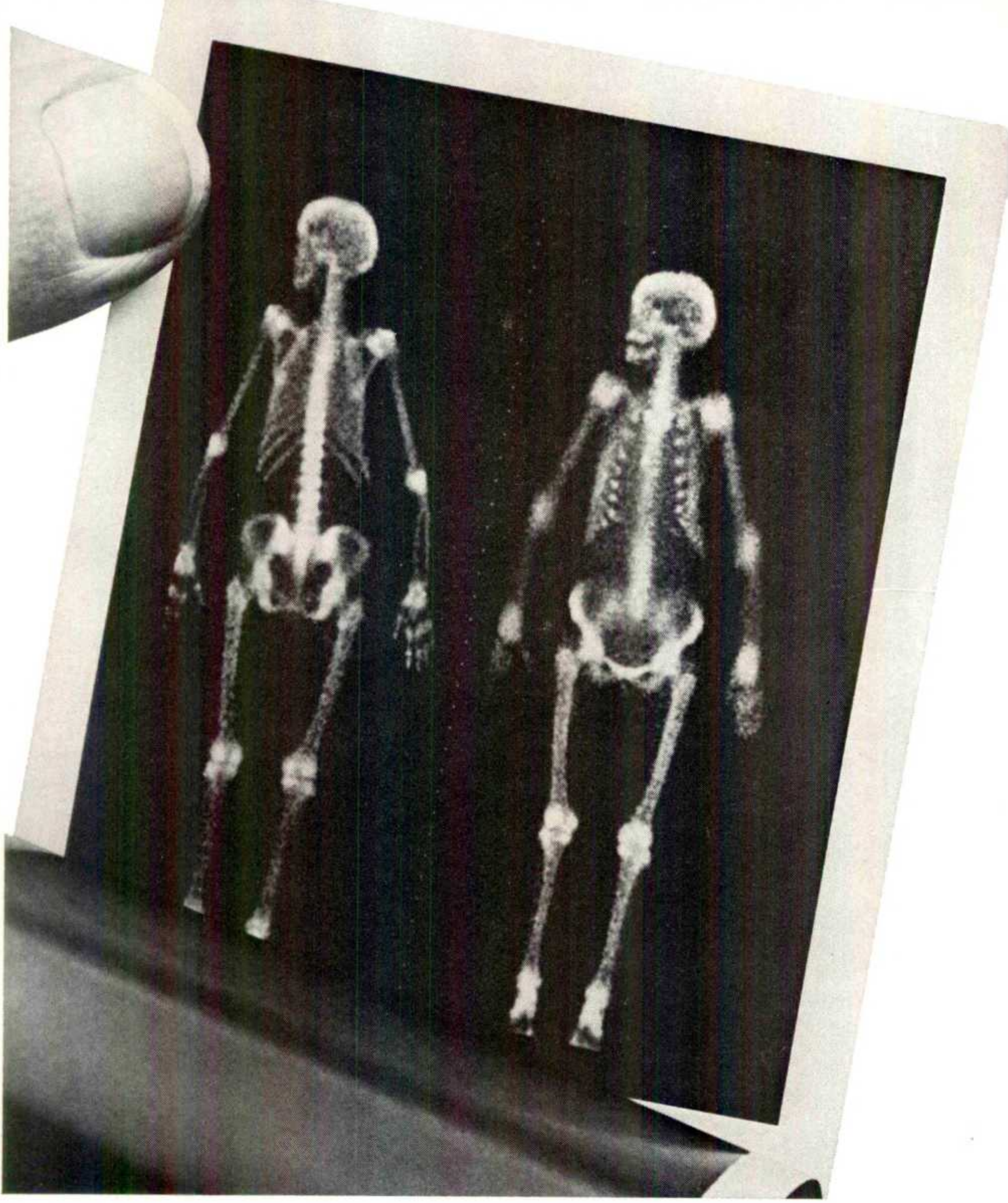

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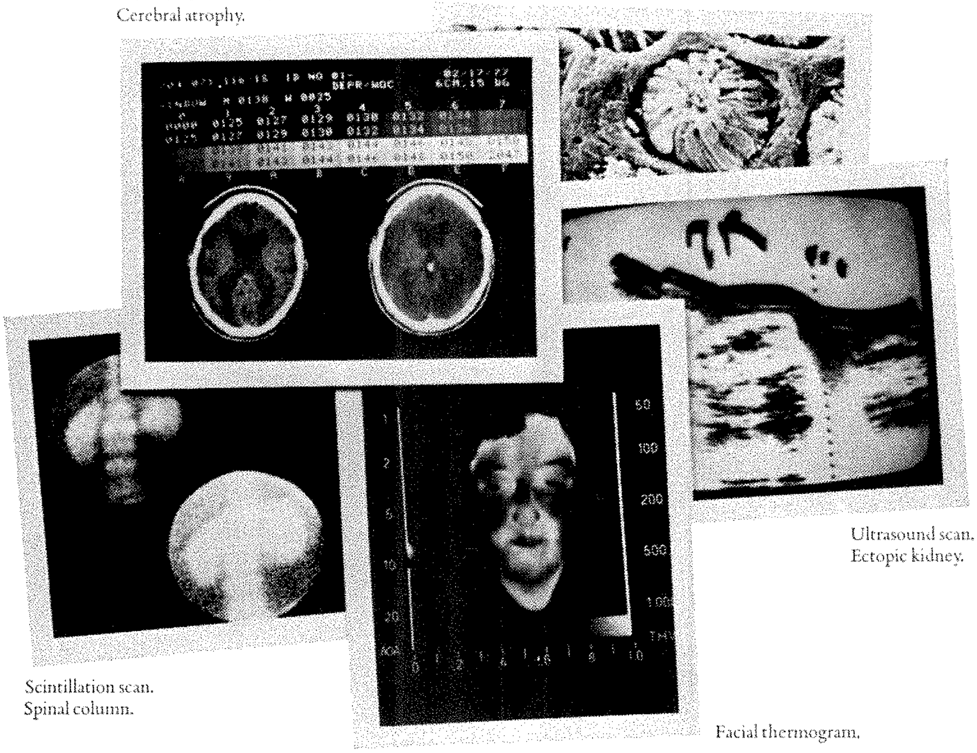

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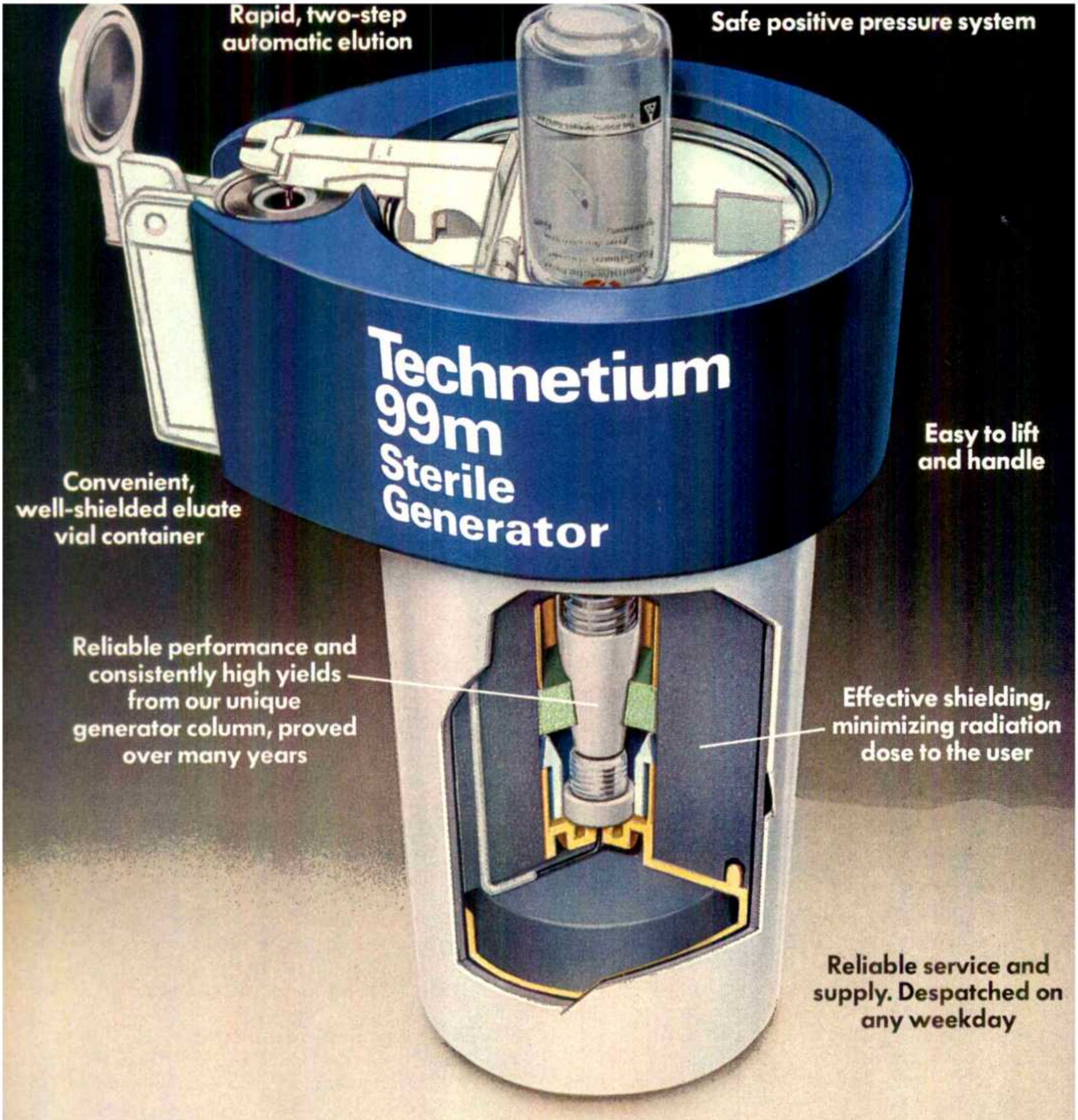

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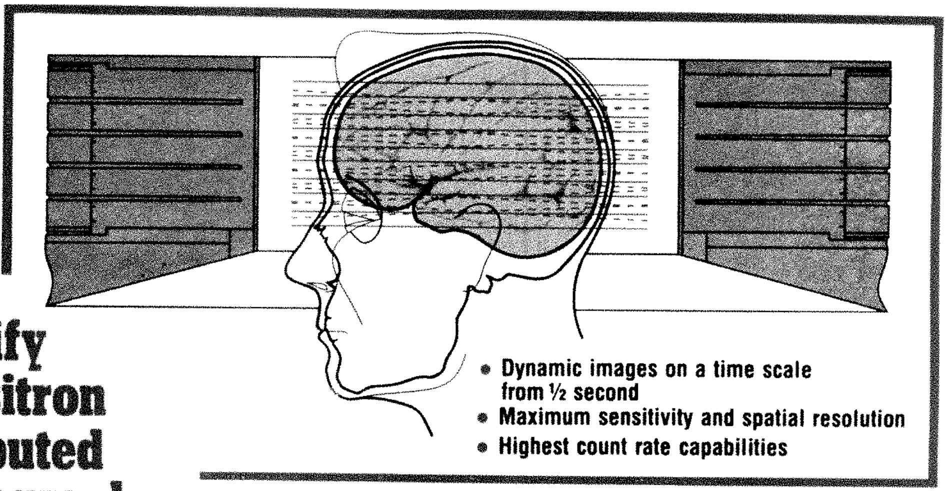

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One major area of concern among researchers has been finding adequate instrumentation to fulfill particular, and perhaps unique, requirements. Instrumentation requirements are dictated by the research application — any tradeoff between sensitivity, resolution, count rate capability and field of view must be carefully weighed in relation to the application at hand. Accordingly, The Cyclotron Corporation has developed its Multi-slice Positron Tomograph systems in varying configurations to fill a growing number of critical needs. Consider, for example, the Model 4600 (one of the three possible systems indicated in the chart below) in which high resolution and count rate capabilities are paramount system parameters. The Cyclotron Corporation welcomes the opportunity to discuss the research physician's unique interests and to configure a system to meet exacting requirements.

Model Number	Application	Number of Simultaneous Image Planes	Geometric Resolution (x, y, z) (mm FWHM)	Average Sensitivity Per Image Plane*	Maximum Useable System Count Rate**
4500	Body	7	10.0	16000	10^6
4600	Neuro	9	8.5	29000	5×10^5
4650	Neuro	7	5.5	16000	3.8×10^5

*Sensitivity expressed as counts/sec per $\mu Ci/cm^3$ for activity uniformly dispersed in 20 cm diameter, water-filled vessel.

**Defined as the "Trues" rate (counts/sec) at which true counts and random counts are equally abundant in the raw data prior to correction and image reconstruction. Tests conducted with 20 cm diameter water-filled phantom extending well beyond detector shield.

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Director
Diagnostic Radiology and Ultrasound
Department of Veterans' Affairs, Queensland

Applications for the above position are invited from suitably qualified medical practitioners who possess relevant postgraduate qualifications and are eligible for registration as a Specialist in Queensland.

The position is located at the Repatriation General Hospital, Greenslopes, which is approximately eight kilometres from the city of Brisbane, the capital of Queensland. Greenslopes is a 550 bed general hospital, affiliated with the University of Queensland as a teaching hospital for medical undergraduates, with Readers and Senior Lecturers in Medicine and Surgery. Accreditation in Medicine, General Surgery, Pathology, Radiology, Psychiatry, Anaesthetics, Dermatology and Rehabilitation has been granted to the hospital.

The department is equipped with modern X-ray equipment. There are eight X-ray rooms and two dark rooms and the department performs 35,000 examinations annually, embracing most of the specialised X-ray procedures. It has a modern, self-contained diagnostic ultrasound division.

DUTIES: As Senior Specialist-in-charge, the successful applicant will be responsible for co-ordinating the work of the speciality of Radiology and Ultrasound within the Branch and advising top level medical and executive management on matters relating to the practice of the specialty.

SALARY: The current salary is $38,131 and there is a right of limited private practice. (At present exchange rate £1=$A1.90)

CONDITIONS: The successful applicant may be permanently appointed as Senior Specialist-in-charge (Radiology), or consideration may be given to fixed term employment for a period of two or three years with the option of negotiating an extension.

Eligibility, subject to medical fitness, for Superannuation benefits

4 weeks annual leave

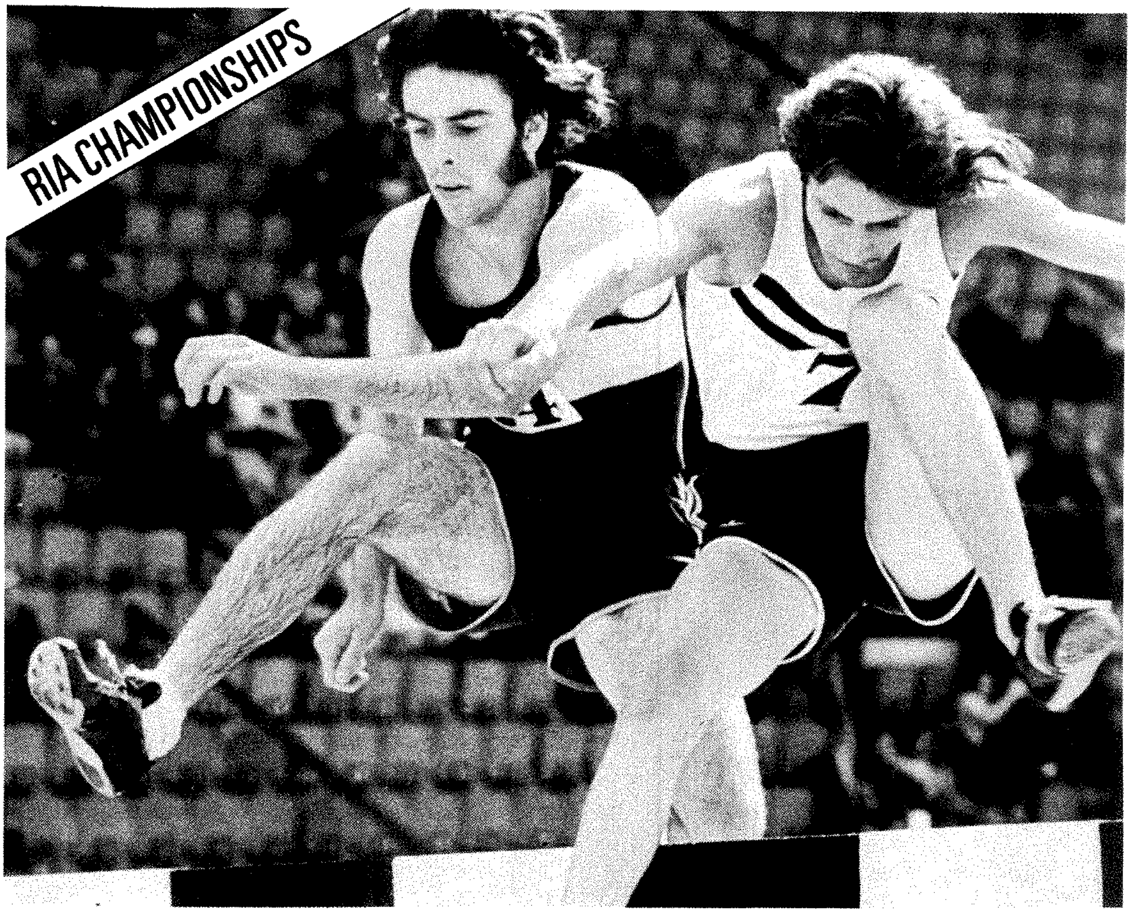
3 months long service leave after 10 years service

Fares to Brisbane for the appointee and family, and an allowance until permanently housed, may be paid. Assistance will also be given towards the removal of household and personal effects.

APPLICATIONS: Applications including details of qualifications and experience, and the names and addresses of three professional referees, should be forwarded to:

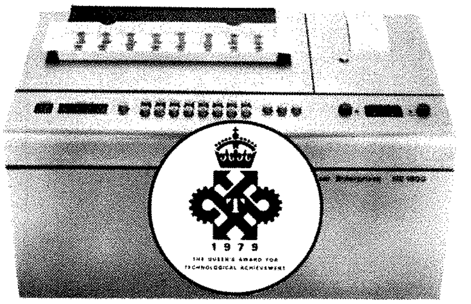
The Deputy Commissioner
Department of Veterans' Affairs
G.P.O. Box 651
BRISBANE QLD 4001

Australia



For its size, the NE 1600 has a great track record

Very high through-put, simplicity of operation, exceptional reproducibility, excellent performance, reliability and compactness are major factors in the world wide success so quickly achieved by NE 1600 ^{125}I/^{57}Co Counter.
In laboratories engaged in routine testing and in research, the outstanding ability of the NE 1600 to count large numbers of samples in a short period of time is widely recognised. A count of 240 typical samples, for 30 seconds each, takes only 8 minutes to complete with the NE 1600, compared with 3 hours 30 minutes in an automatic gamma counter.



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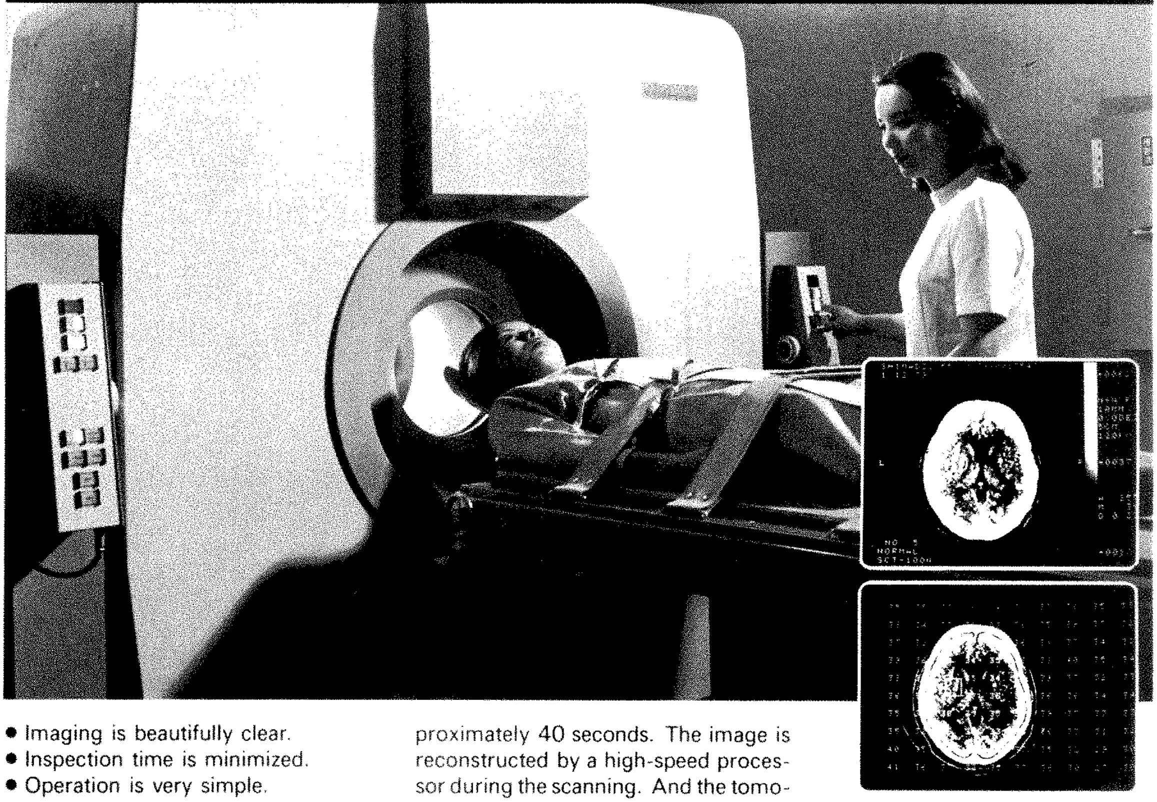
IN ORDINARY TERMS a motorised variable height Bucky table that easily adjusts from a height of 81 cms (32 ins) to as low as 50 cms (19½ ins).

IN CLINICAL FACT a design full of human engineering to help the injured and infirm. A design where patient comfort and safety are essential factors within the specification.

GEC

The Shimadzu SCT-100N 40-Second Rapid Scan

Computerized Axial Tomographic Scanner for Neuroradiology



- Imaging is beautifully clear.
- Inspection time is minimized.
- Operation is very simple.
- A wide variety of software is available.
- The entire system is compact.

Computerized tomography has become an essential part of neurological and emergency diagnosis procedures. And easy-to-operate equipment is especially necessary in emergency applications. The Shimadzu computerized axial tomographic scanner for neuroradiology, the SCT-100N, was developed through long engineering experience to meet just such requirements. The SCT-100N completes scanning in only approximately 40 seconds. The image is reconstructed by a high-speed processor during the scanning. And the tomographic image is displayed immediately after the scanning is completed. Image display is by means of a black and white CRT with a 64-level grey scale and 256 × 256 matrix. The main processor, a mini-computer, makes possible a wide range of practical image processing, including ROI (region of interest), CT number, blinking, enlarged and grid displays.

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Overseas Telex: No.0222-4275 SHMDT J Cable Address: SHIMADZU TOKYO

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4000 Düsseldorf 1, Johannes Weyer Str. 1 F.R. Germany
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Phaedrus made the lion say

Why not the radiologist

The lion in Phaedrus's fable claimed that he had a right to the best, because he was a lion. Likewise, the radiologist is entitled to the best of equipment to perform his task. That is why he is convinced that sheetfilm is the key to top-quality spotfilm photography.
Fortunately, since all leading x-ray equipment manufacturers have opted for the Oldelft 100 mm sheetfilm camera 'Anodica' to complete their image intensifier units, he is guaranteed this top-quality at all times.
There are good and valid reasons for the fail-safe perfection of this camera: conscientious research, design, construction and testing, procedures that were deliberately stretched over years. We left nothing to chance.

Quia nominor leo

Therefore, the 100 mm sheetfilm camera now incorporated in your installation must by sheer definition be the Oldelft Anodica camera (even if it is known by another name, such as Sircam).

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Ultrasound

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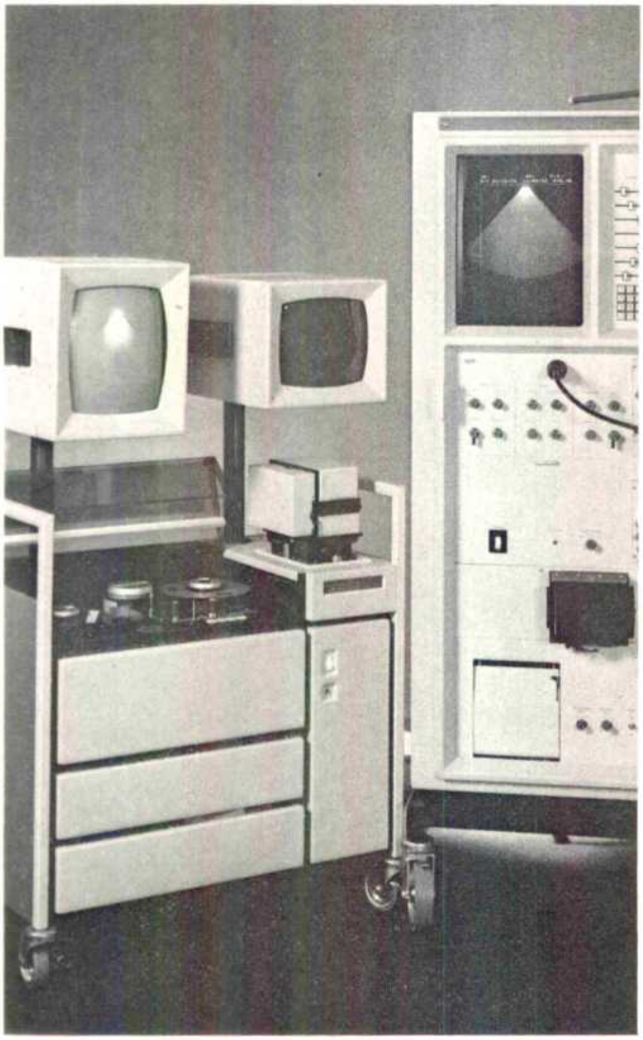
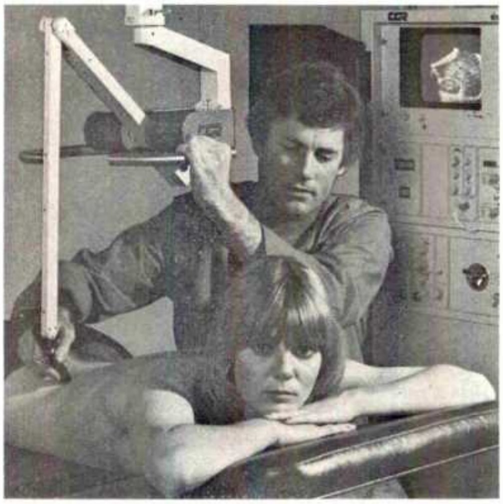
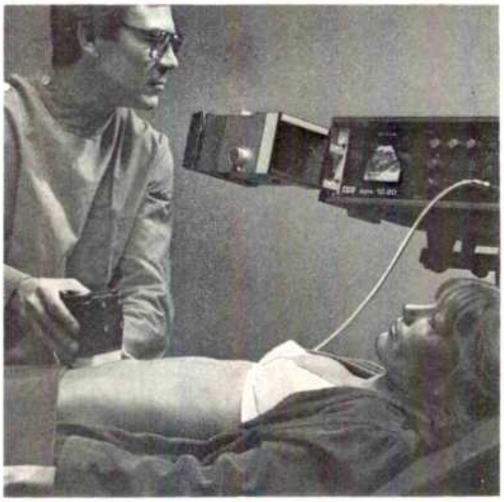


Varian V3000 the ultimate in phased array ultrasonography, with a wide choice of image storing sub-systems.



Generex general purpose scanner for abdominal studies, obstetrics and cardiology.



SMS 10-20 An economic real-time unit with an easily manipulated transducer head.

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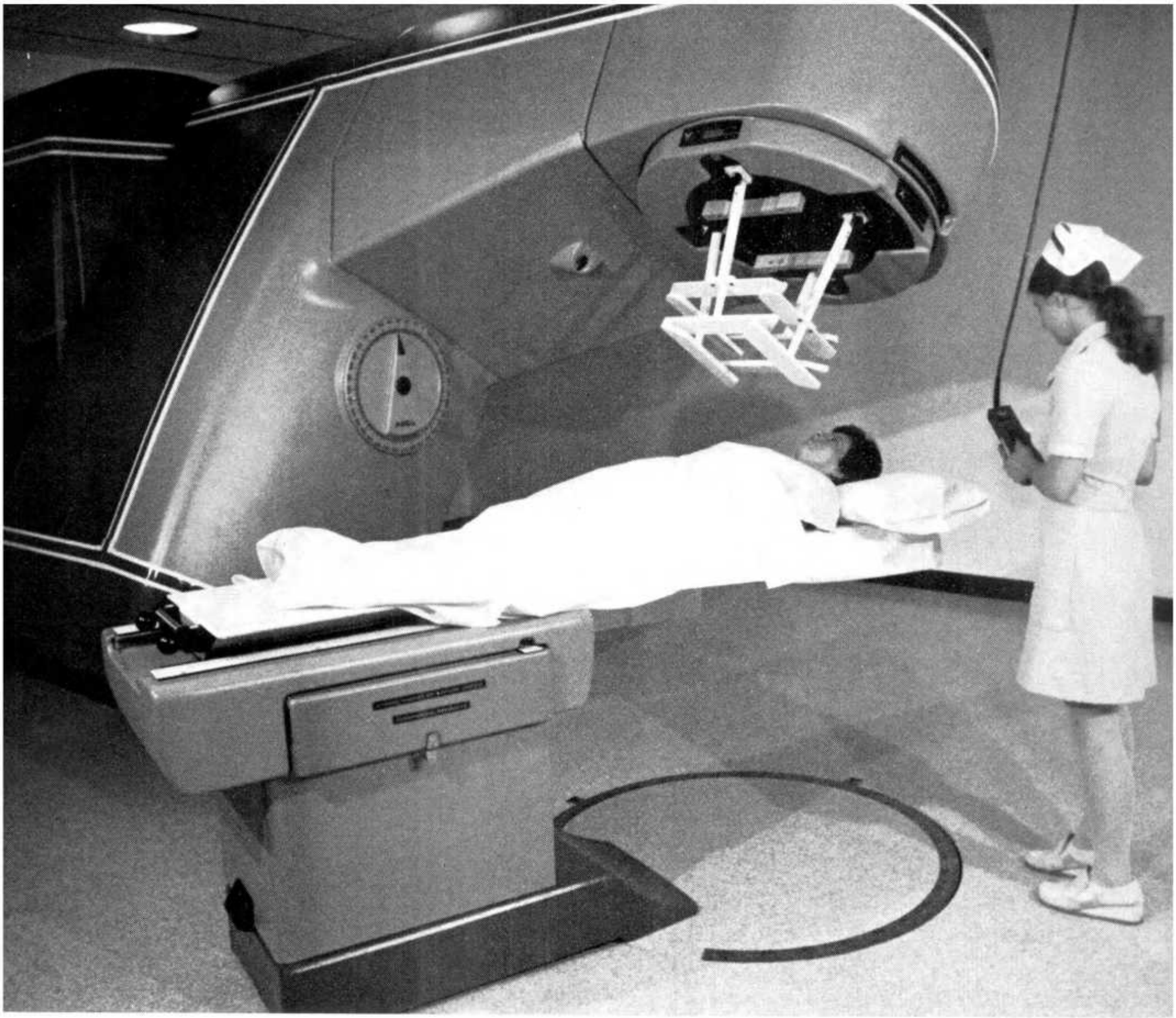

Reliable. Accurate. Unique.

Therac 6 and Therac 20 Linear Accelerators from AECL.

Atomic Energy of Canada Limited presents two ruggedly built, precision engineered linear accelerators which have been designed and proven to deliver years of dependable service — Therac 6 (6 MV photons) and Therac 20 (18 MV photons and 6-20 MeV electrons).

Each possesses a number of unique advantages including large fields in both photon and electron modes, with no primary collimator cut-off. Specific to the Therac 20 is its beam scanning and trimmer bar system which accurately defines infinitely variable electron field sizes up to the largest currently available. Another singular aspect of Therac 20 is the option of dual photon beams which along with the standard electron beams offer exceptional treatment flexibility.

Low isocentric height and high isocentric accuracy are common to both the 6 and 20 as is the 360° collimator rotation with wedged or blocked fields for simplified set-up. Our new, fully motorized accelerator couch features free float on lateral and longitudinal motions. Advanced computer controls with record and verify, superior dose uniformity and depth dose characteristics, and a high, constant output all contribute to maximizing patient throughput.

Your complete satisfaction is assured beginning with our initial sales contact and continuing through architectural planning, installation supervision, final acceptance, and our world-wide 24 hour service support. For full information on Therac 6 and 20, contact AECL — where radiotherapy has been our business for over a quarter of a century.

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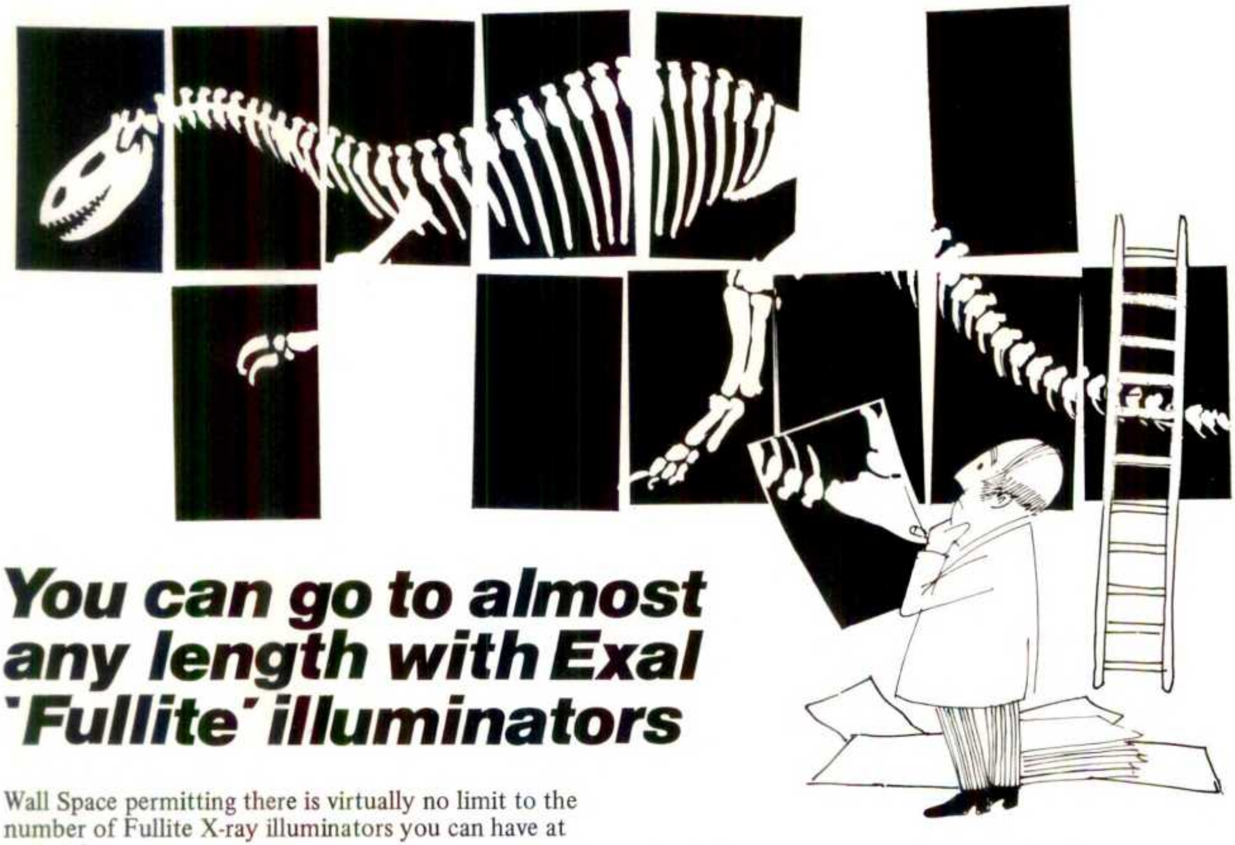


You can go to almost any length with Exal 'Fullite' illuminators

Wall Space permitting there is virtually no limit to the number of Fullite X-ray illuminators you can have at a stretch.

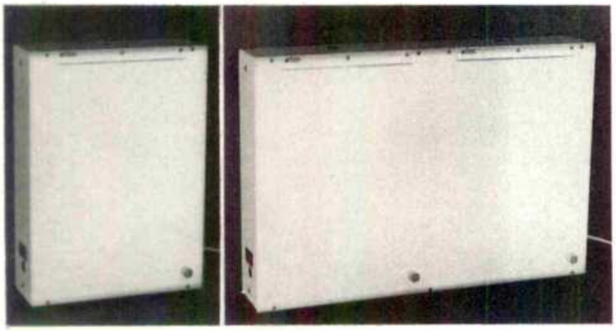
What makes the Fullite so flexible for multiple banking is that each unit has edge-to-edge viewing making it possible to have full surface illumination over the whole bank – no metal frames – no shadows.

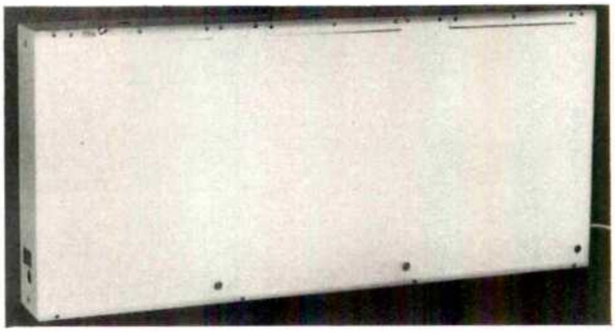
Units are available in three basic sizes – single, double and triple. Standard units are fitted with On/Off switches or they may be supplied with optional Dimmer/On/Off rotary switches. They can also be fitted with high-intensity spotlights.

Fullite units are provided with rubber feet for desk top viewing and key hole slots for wall surface mounting.

Models adapted for inset wall fitting are also available.

Other features include clear plastic film retainers and provision for fitting wet film hanger studs.





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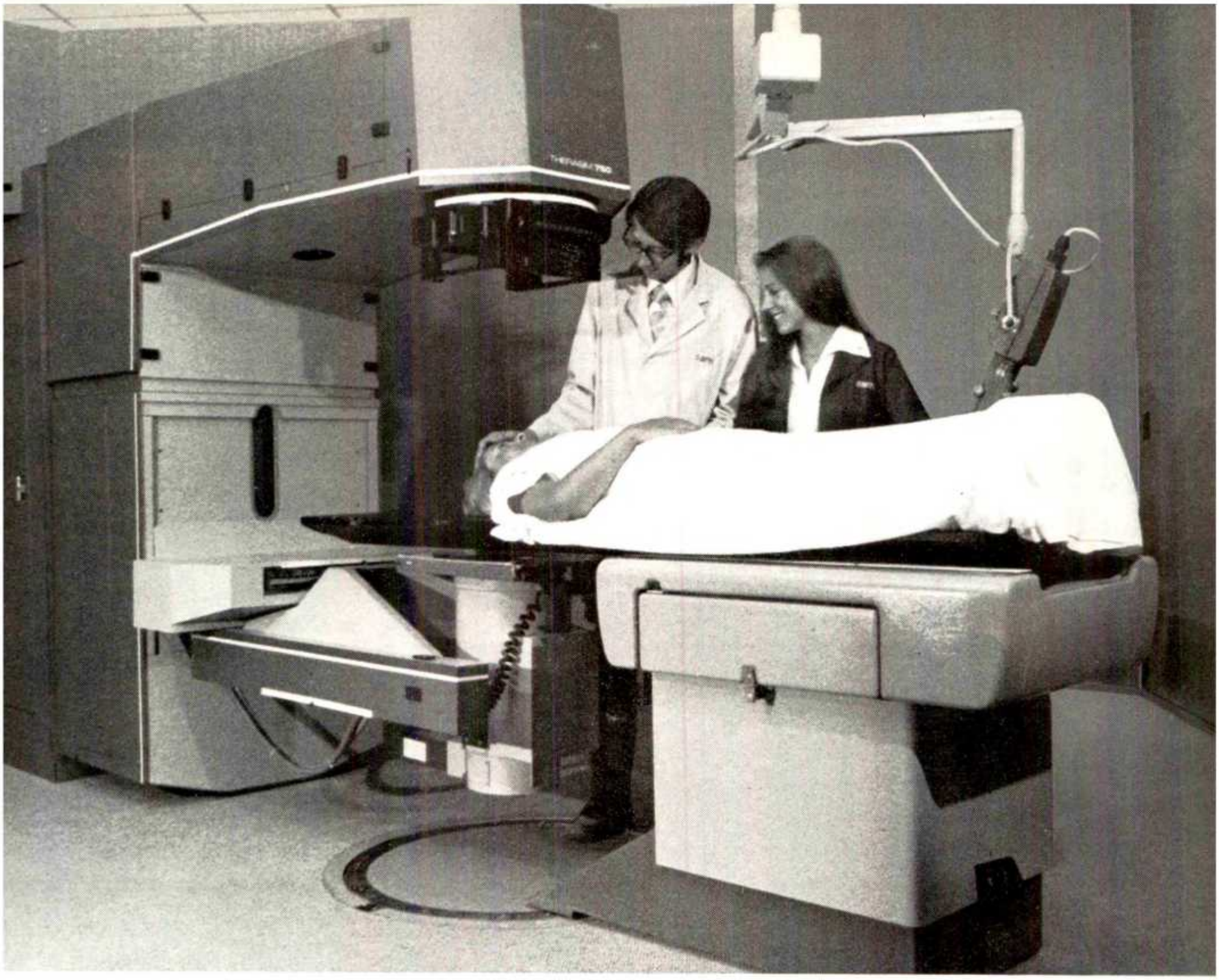
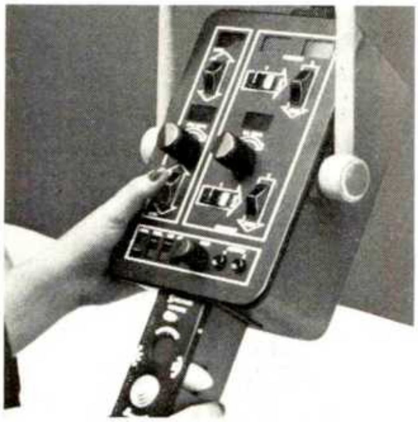


Rugged, Precise, Adaptable
Therasim 750 Universal Simulator from AECL



Therasim 750 Universal Simulator from Atomic Energy of Canada Limited produces the widest possible range of simulation characteristics with rotational radiotherapy units of all type and manufacture. It is particularly compatible with AECL's Theratron 780 and 80 Cobalt units and Therac linear accelerators. In addition, Therasim has been designed to work in concert with computer controlled treatment planning systems such as the AECL TP-11.

With exceptionally rugged frame and carriage construction, Therasim will accommodate the heaviest, high output components while ensuring the ultimate in isocentric accuracy. The image intensifier's extensive travel capability provides the necessary flexibility to cover all conceivable treatment situations and a longer, variable S.A.D. simplifies machine set-up. Therasim 750 permits accurate coverage of large treatment fields in excess of 45cm X 45cm while standard 35.6cm X 43.2cm cassettes are used for storing data. A fully motorized, five motion couch is isocentrically mounted with extra structural rigidity for optimum accuracy of patient set-up. A special stretcher top constructed of carbon fibre is extremely stiff with minimum beam attenuation. Convenient and simple to operate, all Therasim machine functions can be precisely directed from either the local (hand) control within the treatment room or from the console. Both locations feature easy to read, continuous digital displays and backlit panels.

With a quarter of a century devoted to the design and manufacture of advanced radiotherapy equipment, AECL extends the tradition with the Therasim 750 Universal Simulator. For complete information, contact us.

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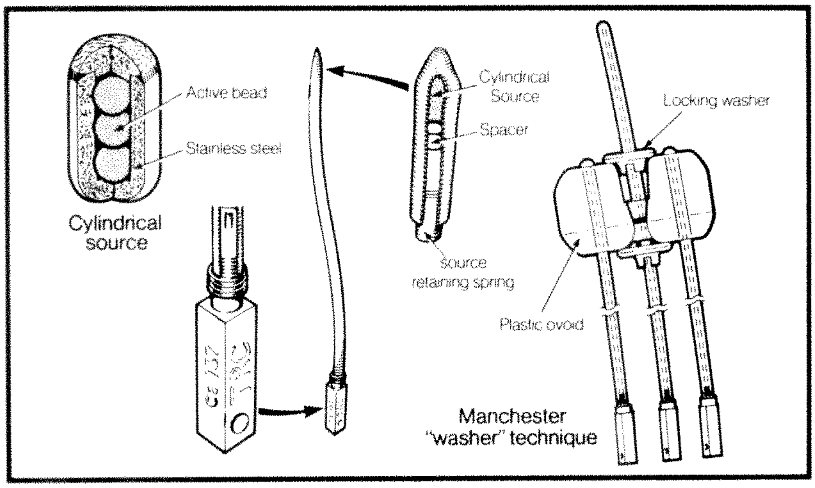
Our Afterloading Systems put brachytherapy right on target

With the addition of our new caesium-137 gynaecological afterloading system, we now supply a comprehensive range of products for intracavitary and interstitial radiotherapy.

Intracavitary radiotherapy

Our caesium-137 "Manchester" afterloading system consists of X-Ray opaque PVC applicators which allow the "washer," "spacer" or "tandem" techniques to be used. The guide tubes are flexible and have a diameter of only 6.3 mm overall. Complete kits are supplied sterilized in packaging designed for maximum convenience in use.

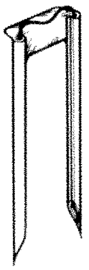
The sources contain glass beads in welded stainless steel capsules assembled into flexible source trains for which special shielded containers are supplied. Iso-dose curves are available for each source train. Individual sources and source trains are also supplied for most of the currently available remote afterloading systems.



Interstitial radiotherapy

Our iridium-192 flexible wire afterloading systems include complete sets of applicators and accessories for the Pierquin/Paine technique. All accessories for these systems are pre-packed ready for use and sterilized where necessary. Platinum clad iridium-192 wire in 500 mm lengths is readily available in activities up to approximately 0.3 mCi/mm providing exposure rates of up to 0.16 mR per hour at 1 metre.

Iridium-192 "hairpins" and single pins: Thicker platinum coated iridium-192 wire is supplied pre-shaped as "hairpins" and single pins for use with slotted guide needles which are made in stainless steel to the designs of Pierquin and Paine.



The Radiochemical Centre
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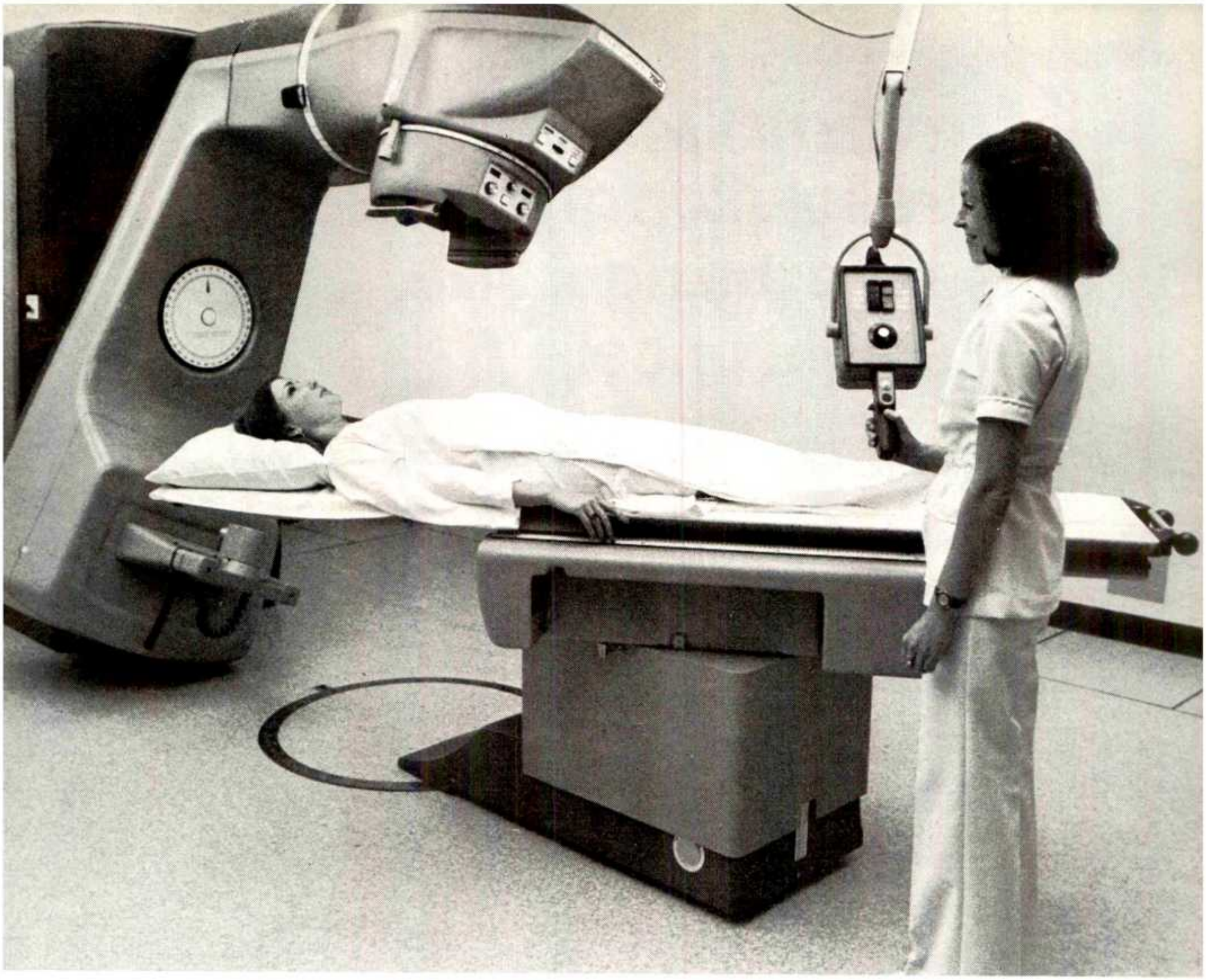

Dependable. Versatile. Economical.
Theratron 780 Cobalt 60 Unit from AECL.

The Theratron 780 Cobalt 60 unit is a powerful combination of dependability and versatility from Atomic Energy of Canada Limited. Sturdily constructed, it has low maintenance and shielding requirements, and represents a highly reliable, trouble-free concept of teletherapy treatment at low capital cost. The reliability of AECL cobalt therapy equipment is best exemplified by the fact that 8 of our original units, built over 25 years ago, still remain in service.

The versatile Theratron 780 allows you to match the source (and cost) to your specific clinical needs, all the way up to 200 rmm. For example, a small clinic with a light patient load could use a correspondingly small source. Primarily known for its effectiveness at superficial and medium depths, Theratron 780 is capable of effective treatment at all depths. Since its beam is essentially monochromatic, resulting in minimal skin reaction, it is frequently the number one choice for head and breast treatments. A fully motorized couch with free float on lateral and longitudinal motions enables quick set-up, optimizing patient throughput. In addition, a large variety of optional accessories are available to suit your specific treatment procedures.

AECL is your comprehensive centre for all your teletherapy treatment needs. Every aspect is efficiently covered from our initial sales contact through architectural planning, installation supervision, final acceptance, to our world-wide, 24 hour, service support. What's more, we manufacture and load the sources. In fact, over 3000 AECL beam therapy sources have been supplied to the international marketplace. For full information on Theratron 780 or any other product, contact AECL — where radiotherapy has been our business for over a quarter of a century.

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Comparable to the best multi-format cameras.

Scans can be adjusted to highlight areas of interest without guess work or waiting on wet-process film development. And with the big 500 foot paper rolls, there is rarely a wait for reloading.

We've also made the 4634 easy to incorporate in a system. And cost per copy is unusually inexpensive.

The 4634 is sold exclusively through OEM system builders.

For further information and full specifications contact:—
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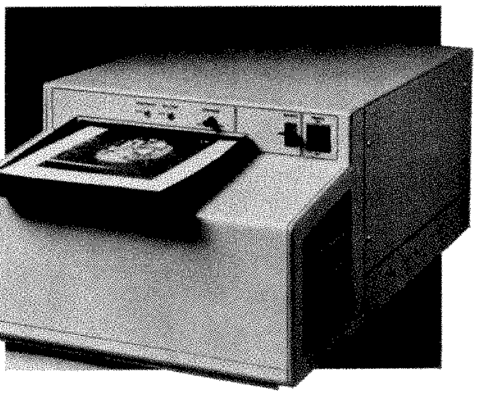

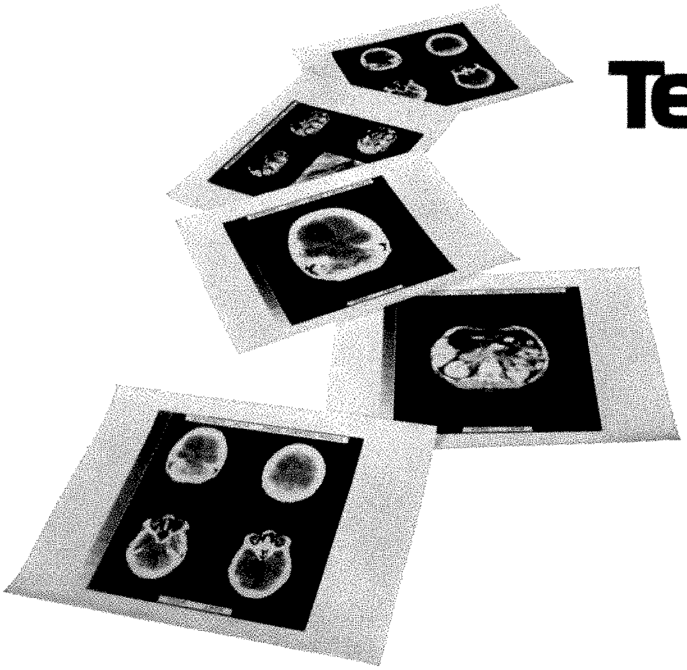

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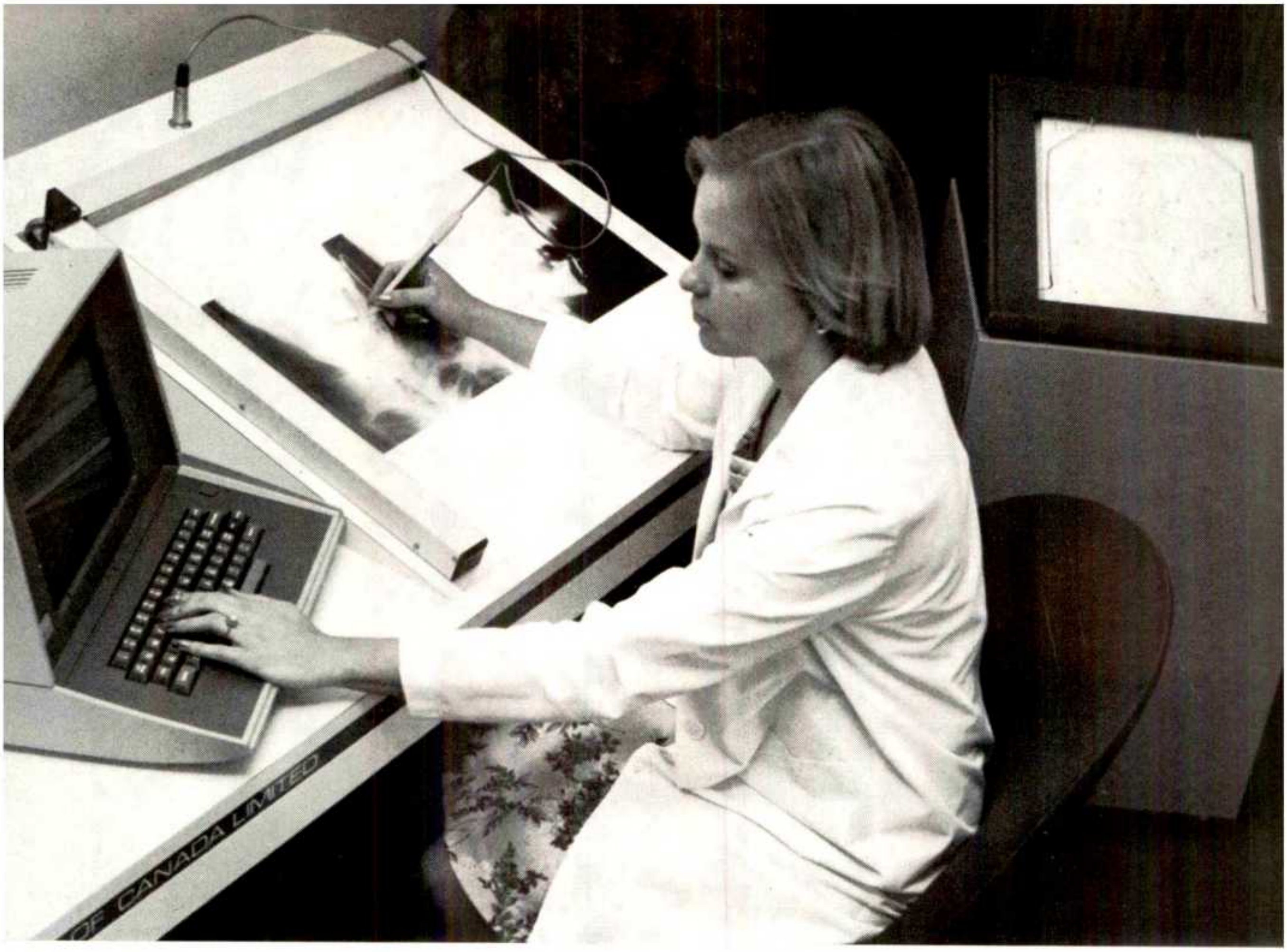
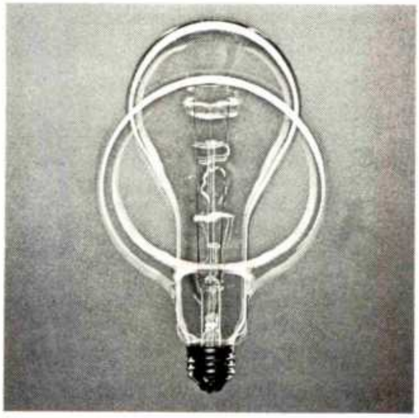


Simultaneous treatment planning and information management.
TP-11 and TRIM from AECL.



Atomic Energy of Canada Limited has taken two ideas and made them work better as one. The resulting combination allows, for the first time, simultaneous treatment planning and information management.

Half the combination is TP-11, an interactive, computerized, radiotherapy planning system which eliminates the need for tedious and often imprecise manual planning. It is capable of a wide variety of plan calculations utilizing a virtually unlimited number of beams. Dose distributions are rapidly calculated for fixed and moving rectangular photon and electron beams, irregular photon beams, and brachytherapy plans, using both point and linear sources. All plan types may be combined without practical limit. In addition, rapid modifications may be easily made, enabling the operator to select the optimum plan from a visual display. A hard copy plot can be produced and the plan is automatically stored. Included in the system is high quality PDP-11 computer hardware and a 50.8cm x 50.8cm sonic digitizer with sparking stylus for entry of graphic data.

TRIM, the Tumour Registry and Information Management system, forms the other half of the combination. Of particular benefit to the radiologist and epidemiologist, it represents a unique, interactive, multi-user approach to clinical data management. A complete and self-contained software system, TRIM can be used to enter, update, delete, and selectively retrieve patient data according to the specific needs as described by its user. Additional features include a readily expandable data base which can be customized to suit the user's requirements and software programs which allow transfer of data to a central data base.

Although both TP-11 and TRIM can operate independently of each other and in conjunction with other systems, they reach their maximum potential when used together and with AECL's broad range of radiotherapy equipment. For full information on how TP-11 and TRIM can bring added dimensions of accuracy to your treatment planning and record keeping, contact AECL.

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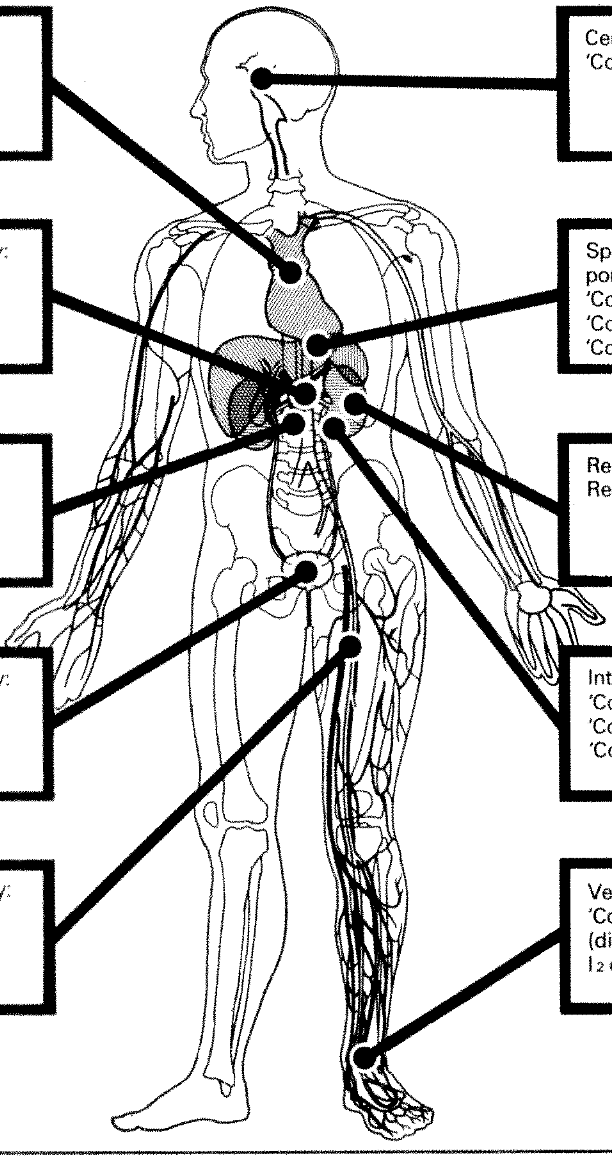

Angio-cardiography:
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'Conray 420':
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Abdominal-aortography:
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'Conray 325':
Cardio – 'Conray'

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'Conray 420':
'Conray 325'

Retrograde pyelography:
Retro – 'Conray'

Intravenous urography:
'Conray 325':
'Conray 420':
'Conray 280'

Venography:
'Conray 280'
(diluted to 150–200 mg I_2 equivalent)

Conray Contrast Media

(Meglumine and sodium iothalamate)

No matter what your particular requirements may be, there is almost certainly a presentation suitable. If you are in any doubt whatever, contact your May & Baker representative or telephone our Medical Information Department (01-592 3060)

Full information supplied on request

'Conray' is a trade mark of Mallinckrodt Inc.

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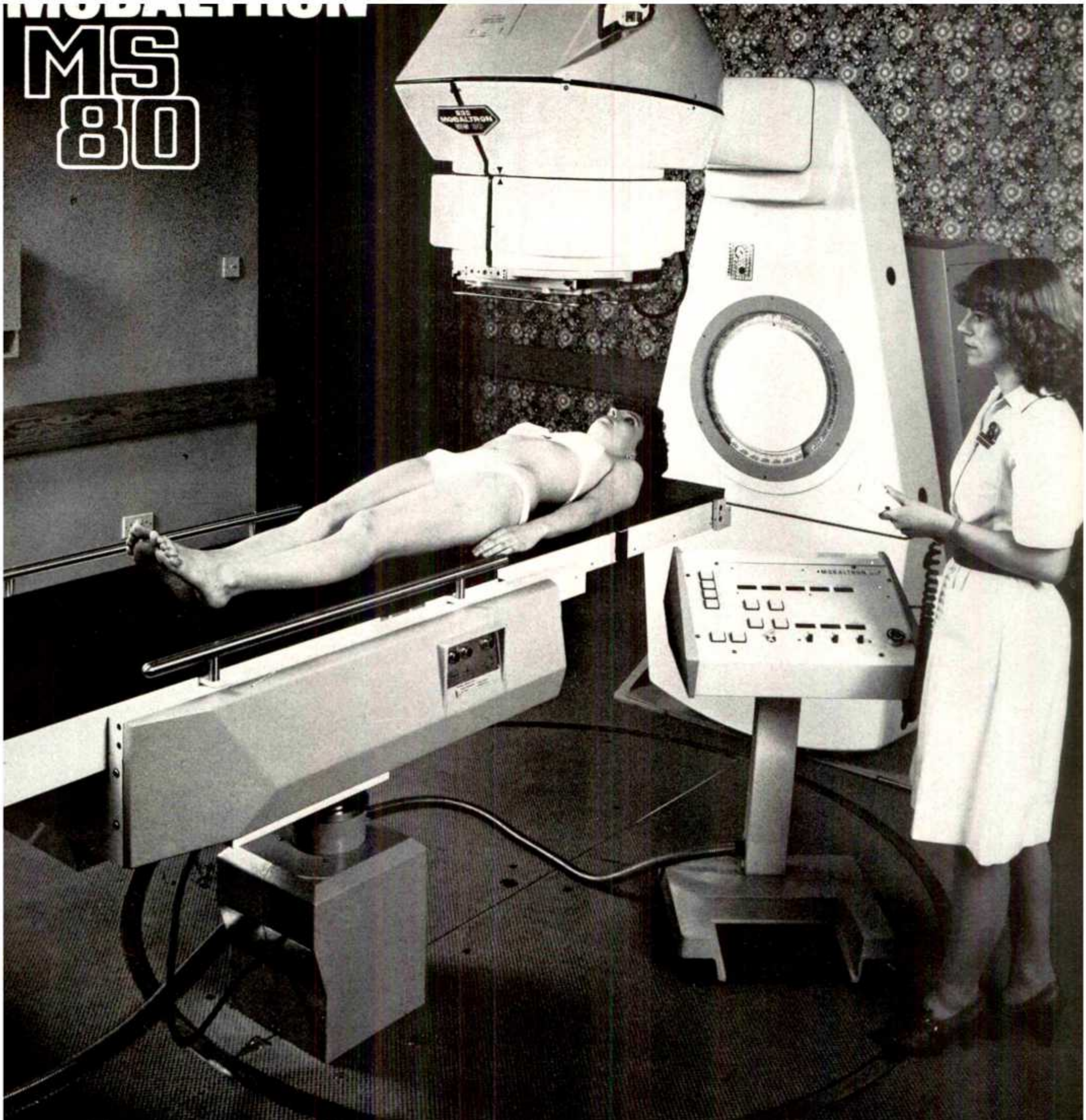
MOBALTRON
MS 80



The Mobaltron M S 80 is one of the most sophisticated cobalt 60 units in the world, complying fully with R.A.S.M.P. 75 and having the following features:

- 40 x 40 cm field size at 80 cm.
- 10,000 RHM head capacity.
- Full interlock and confirmation circuits.
- Digital readouts.
- Dual timer.
- Variable speed motorised movements.
- Split spine treatment table.

The Mobaltron M S 80 can also be supplied as a computer controlled tracking unit.

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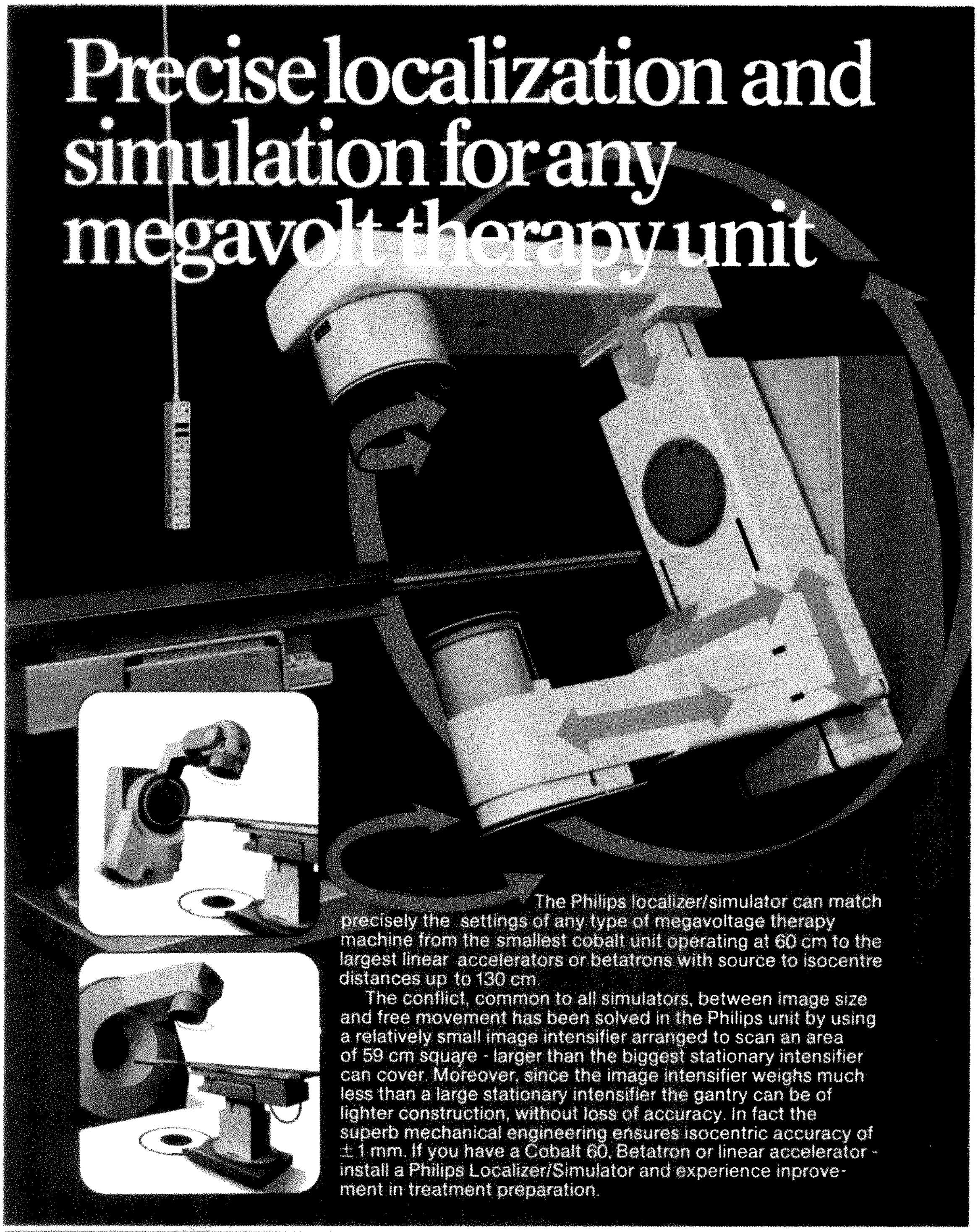
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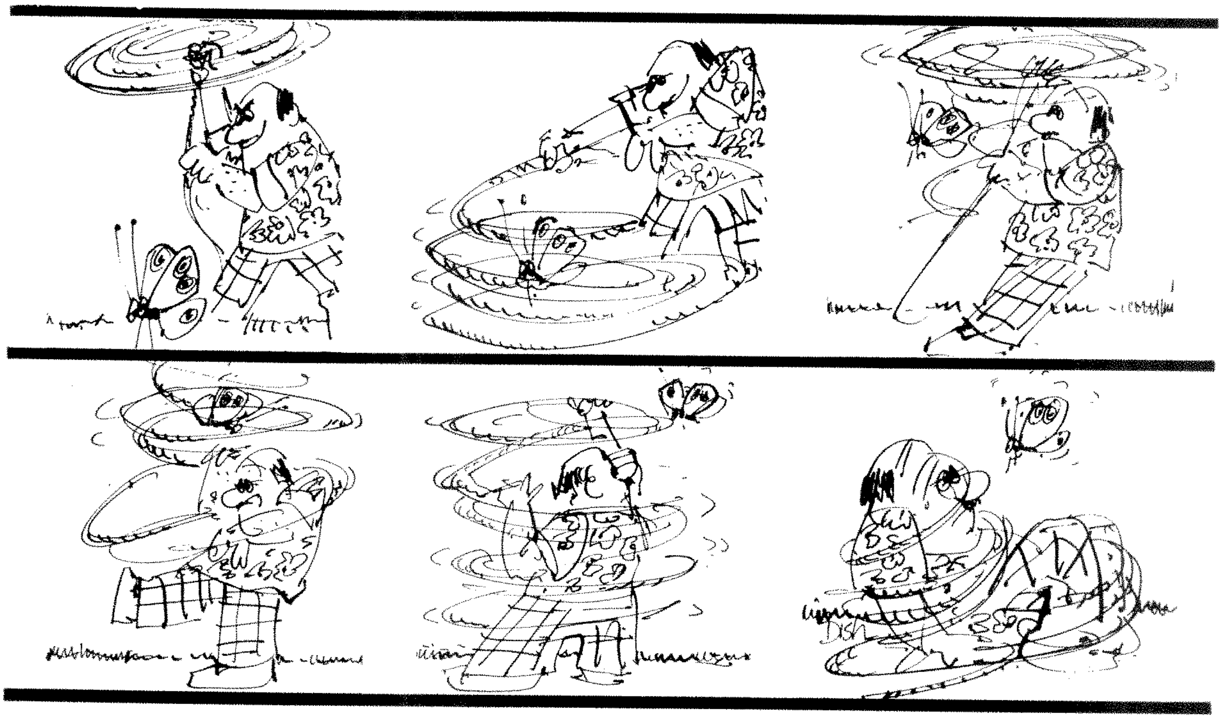

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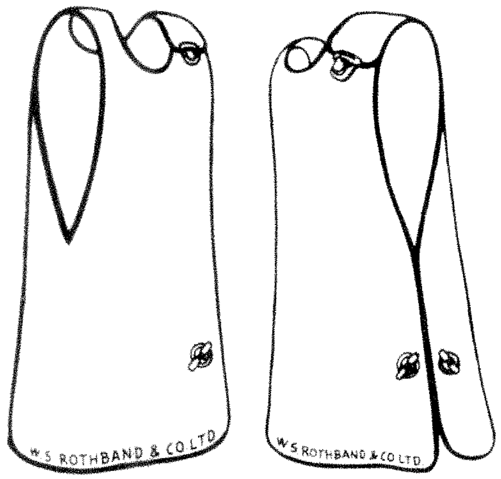
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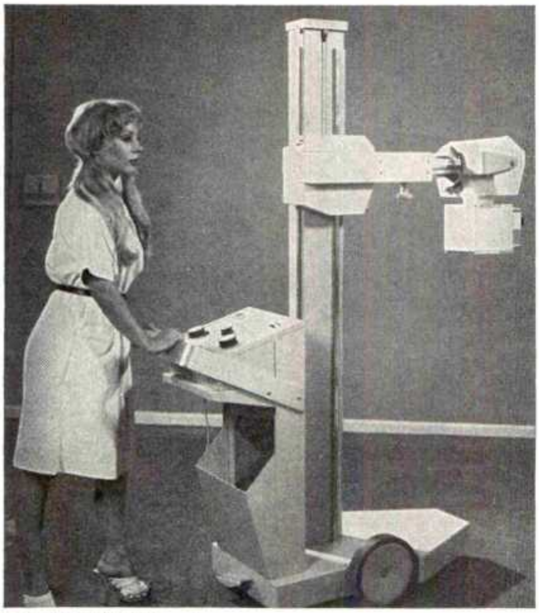

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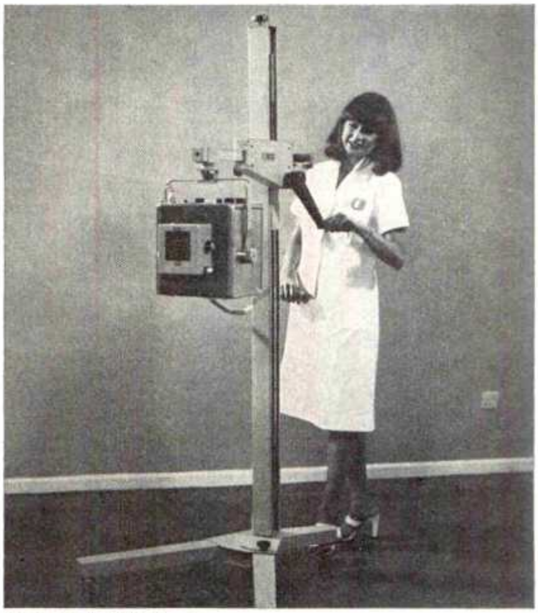

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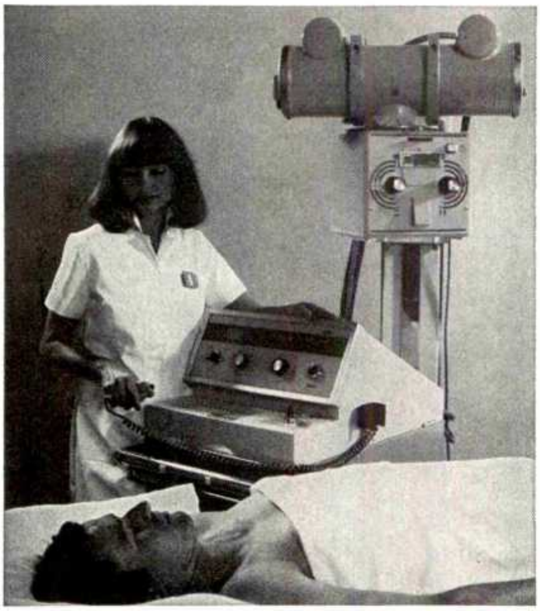

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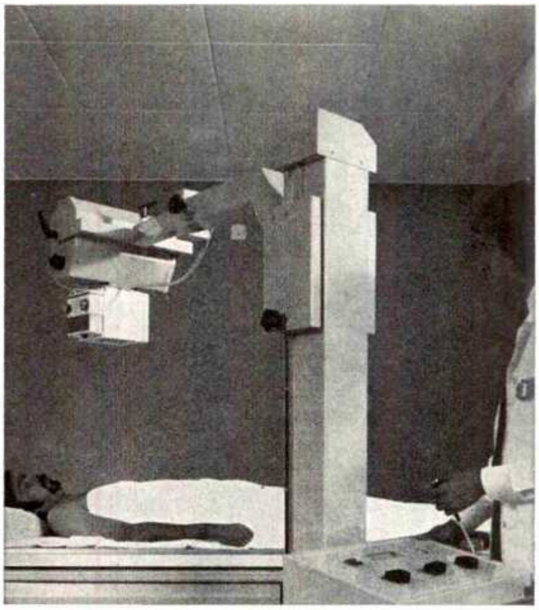

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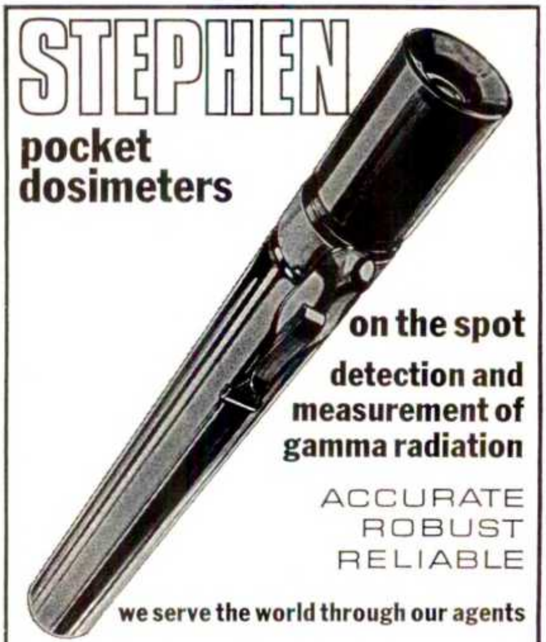

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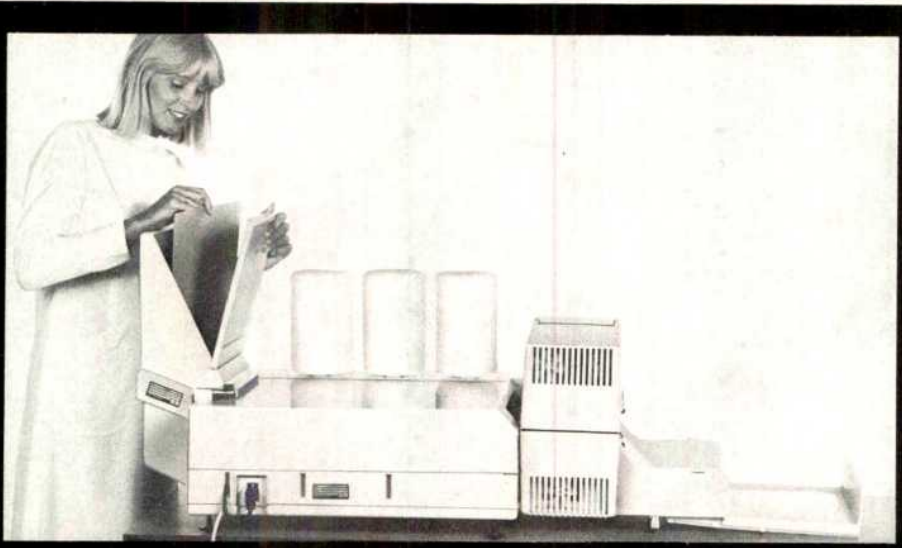

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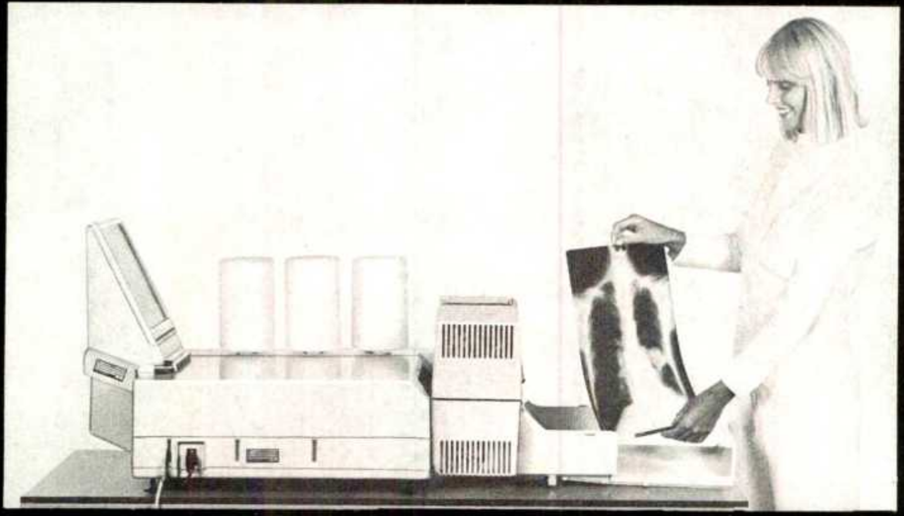

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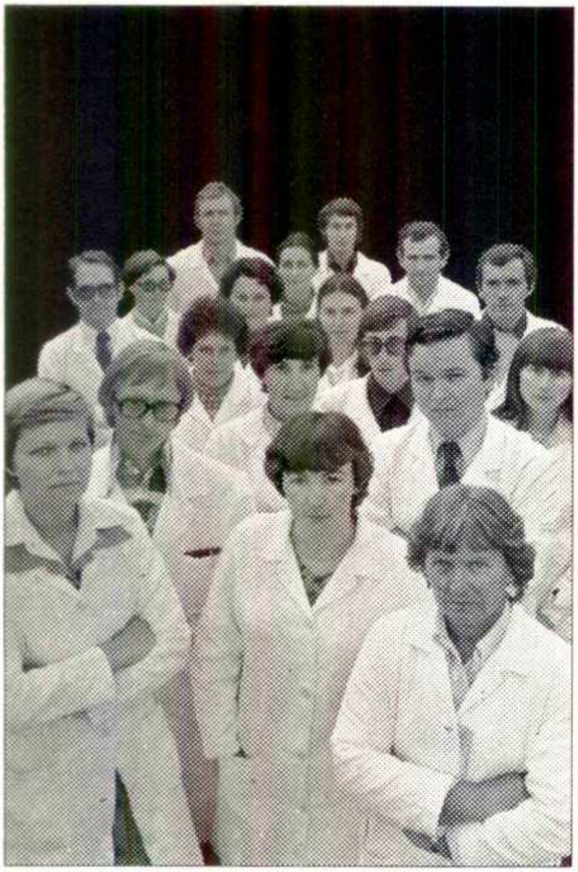

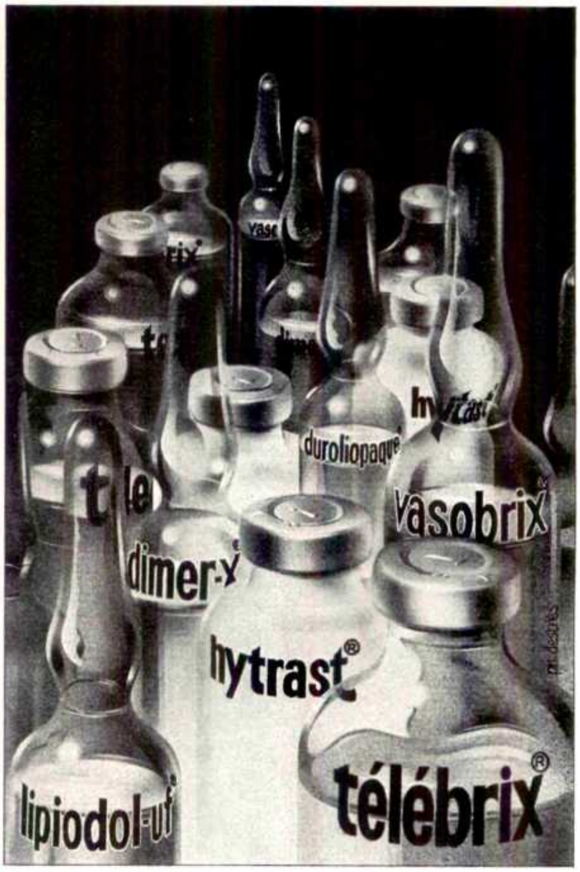

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The British Journal of Radiology

Angiographic appearance of post-operative aortic valvar stenosis. Angiographic and haemodynamic correlation

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(*Received February 1979*)

ABSTRACT

The classic angiographic appearance of a stenotic aortic valve is that of "doming". Adequate relief of the obstruction can be obtained with an aortic valvotomy. It should be stressed, however, that even in the absence of an haemodynamically significant gradient, "doming" of the aortic valve persists over many years and is explained by the presence of an anatomically bicuspid valve.

The angiographic appearance of the aortic valve after surgical valvotomy has not been described in the numerous reports of the haemodynamic findings following surgery. Since the angiographic appearance may give rise to misinterpretation, a retrospective angiographic-haemodynamic study was carried out.

MATERIAL AND METHODS

The pre- and post-operative haemodynamic measurements and the angiographic appearance of the aortic valve in 21 patients are the subject of this report (Table I). The ratio of males to females was 12:9; the age range was from six to 14 years; 18 of the aortic valves were bicuspid and three unicuspid. The pressure gradients across the aortic valve after the surgical valvotomy were:

gradient of 0 in 3 patients;
gradient of < 35 in 4 patients;
gradient of 35–60 in 10 patients;
gradient of > 60 in 4 patients.

In all of the patients there was doming of the aortic valve pre- and post-operatively with demonstration of aortic reflux in 16 patients of varying magnitude. The average interval between surgery and the follow-up study was one year.

DISCUSSION

Despite numerous reports of the haemodynamic findings following aortic valvotomy, no emphasis has been placed on the angiographic appearance of the aortic valve following the surgical procedure (Braunwald *et al.*, 1963; Lees *et al.*, 1962; McGoon *et al.*, 1969; Morrow *et al.*, 1963). As our study proves, all of the valves "dome" postoperatively, even in cases with no pressure gradient (Fig. 1). The only angiographic difference is the size of the "jet" of contrast medium which is larger in the post-operative patient due to the increased valve orifice.

The persistence of angiographic "doming" after valvotomy cannot be correlated with persistent haemodynamic obstruction at the valve level in the majority of our patients (12/21). "Doming" of the aortic valve persists over many years, as was demonstrated in the patients with the longer follow-ups.

Angiographic "doming" of the aortic valve is related to the short length of the two free edges of leaflets that are the end result of the surgical correction (Fig. 2). The valve remains anatomically either uni- or bicuspid. Since the free edge of a bicuspid valve does not have enough length, it cannot open completely during systole and approximation of the leaflet with the arterial wall cannot occur as in the normal valve (Fig. 3). Even though an adequate haemodynamic result has been achieved as demonstrated by the absence of haemodynamically significant gradient, bicuspid and unicommissural valves remain anatomically stenotic even after surgery.

CONCLUSION

The angiographic appearance of "doming" of the aortic valve following successful valvotomy is a constant finding together with persistence of the poststenotic dilation of the ascending aorta. The presence of "doming" does not imply the absence or

TABLE I

HAEMODYNAMIC, SURGICAL AND ANGIOGRAPHIC FINDINGS

Patient number	Age/sex	Follow-up interval	Haemodynamic measurements		Anatomic appearance of aortic valve
			Pressure gradient	Aortic reflux	
1	12/F	1 year	60 mm	No AI	Unicuspid
2	11/F	1 year	58 mm	No AI	Bicuspid
3	9/M	19 months	None	2+AI	Bicuspid
4	15/M	15 months	36/52	No AI	Bicuspid
5	14/F	15 months	None	3+AI	Bicuspid
6	15/F	16 months	30/65	No AI	Bicuspid
7	16/M	1 year	None	2+AI	Bicuspid
8	15/M	15 months	35/55	2+AI	Unicuspid
9	15/F	1 year	None	2+AI	Bicuspid
10	15/F	2 years	34/60	2+AI	Bicuspid
11	13/F	1 year	20/20	1+AI	Bicuspid
12	6/M	1 year	64 mm	2+AI	Bicuspid
13	13/M	8 months	25/40	1+AI	Bicuspid
14	6/F	1 year	23/38	No AI	Bicuspid
15	11/M	1 year	25/50	2+AI	Bicuspid
16	13/M	2 months	30/50	2+AI	Bicuspid
17	17/M	9 years	25/20	3+AI	Unicuspid
18	15/F	5 years	20/35	2+AI	Bicuspid
19	16/M	16 months	20/60	2+AI	Bicuspid
20	9/M	13 months	5/20	1+AI	Bicuspid
21	8/M	7 months	35/50		Bicuspid

Angiographic appearance of post-operative aortic valvar stenosis. Angiographic and haemodynamic correlation

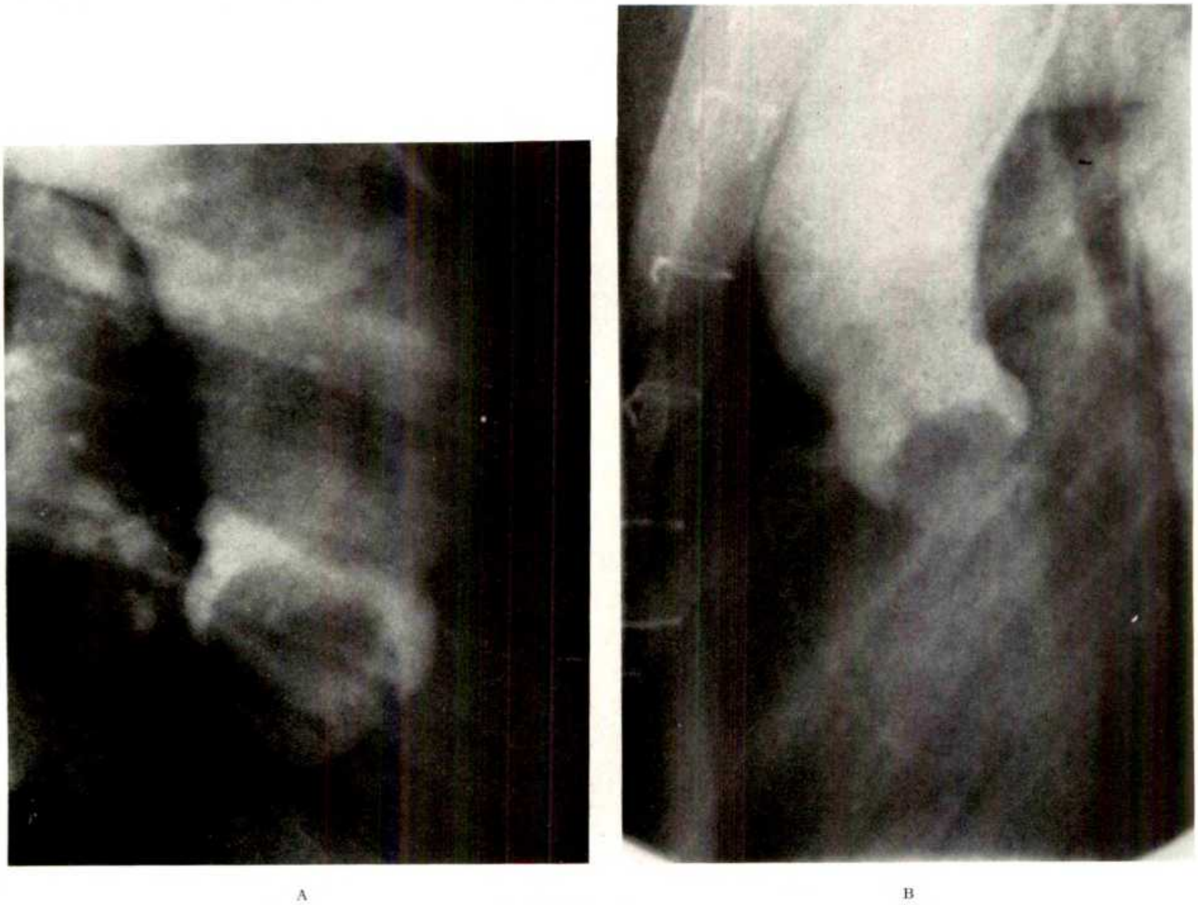

FIG. 1.

(A) Aortogram reveals "doming" of a bicuspid aortic valve with post-stenotic dilation of the ascending aorta (Case 3).
(B) Postoperative aortogram reveals persistent "doming" of the aortic valve and of the poststenotic dilation after an adequate relief of the obstruction (Case 3). No gradient.

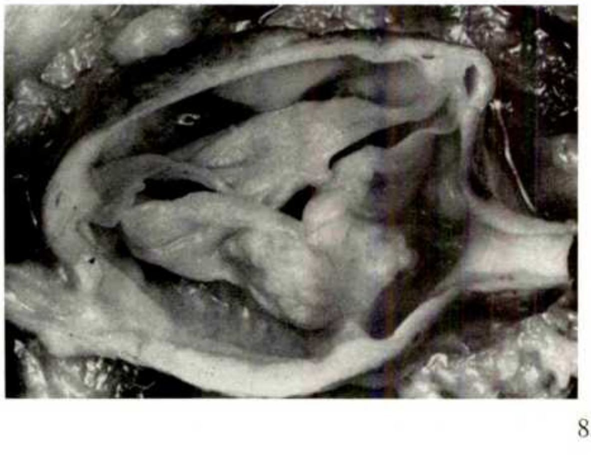

FIG. 2.

Photograph of a specimen after valvotomy. Patient died of unrelated causes years after surgery. There was a bicuspid aortic valve with thick, rolled edges of the leaflets, which are of short length, as compared with the calibre of the aorta at the same level.

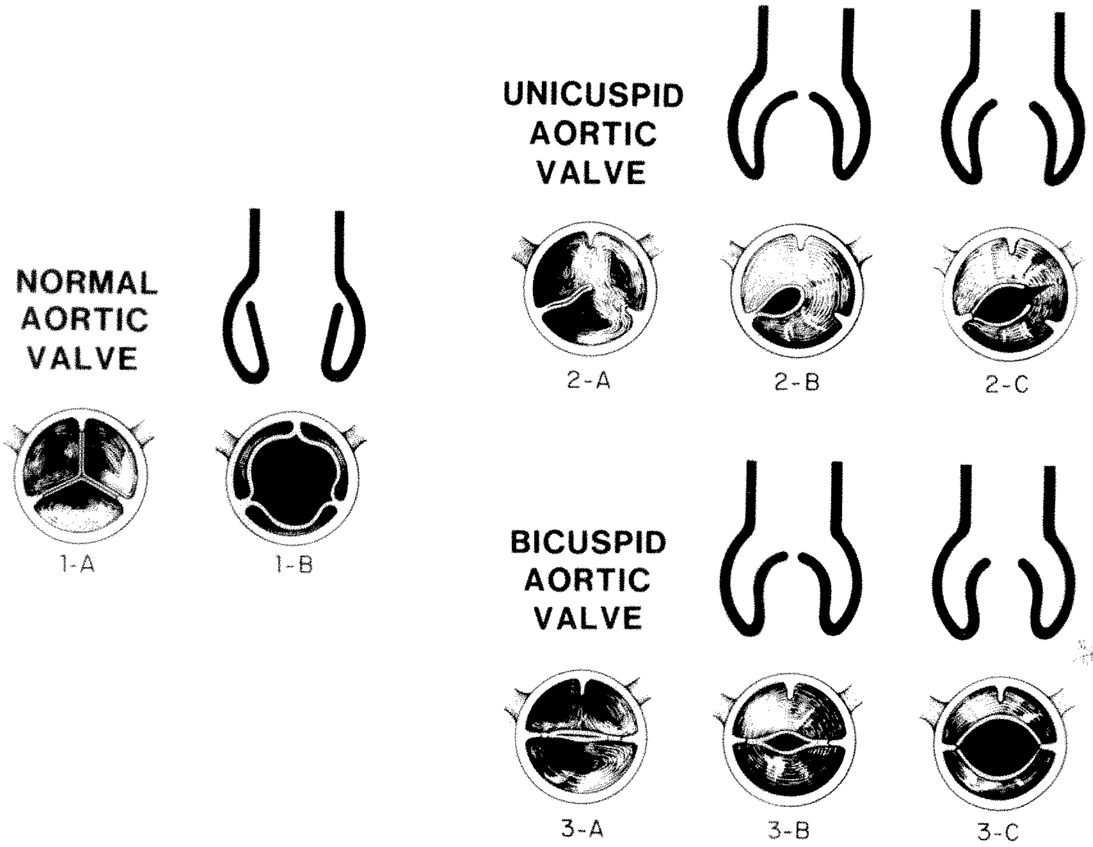

FIG. 3.

(1–A and 1–B). Normal aortic valve in closed (1–A) and open (1–B) positions. Note the redundancy of the valve leaflets in the open position. Sagittal section of an open valve. Note the apposition of the leaflet with the arterial wall.

(2–A, 2–B, 2–C). Cross section of unicuspid aortic valve in closed (2–A) and open (2–B) positions; sagittal view in open position. Postoperative appearance is that of a bicuspid valve (2–C). Sagittal view reveals "doming" of the valve leaflets with widening of the opening.

(3–A, 3–B, 3–C). Cross section of the bicuspid aortic valve in closed (3–A) and open (3–B) positions. Note the slit-like opening produced as a result of the short length of the free edges of the valve leaflets; thus, the valve is unable to open completely during systole (3–B). Sagittal view of an open bicuspid valve shows the characteristic appearance of a "doming" valve (3–B). The surgical procedure simply widens the opening, but a bicuspid valve is still present (3–C). The sagittal view postoperatively reveals persistent "doming" but widening of the opening (3–C).

presence of an haemodynamically significant gradient across the valve. It should not be considered as a sign of persistent obstruction at the valve level following surgery.

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The left atrial notch: a sign of persistent left superior vena cava draining to the right atrium

By J. P. Owen, M.B., B.S., D.M.R.D., F.R.C.R.

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(*Received May 1979*)

ABSTRACT

A notch in the inferior border of the left atrium has been observed in patients with a persistent left superior vena cava draining via the coronary sinus into the right atrium. It is suggested that the notch is due to the dilated coronary sinus.

Persistence of the left superior vena cava (LSVC) is encountered in a number of children with congenital heart disease and its pre-operative diagnosis may be important to the cardiac surgeon. For example, in patients undergoing open-heart surgery by extra-corporeal by-pass an unsuspected LSVC could result in a troublesome inflow of blood into the right atrium. The presence of a LSVC and left innominate would allow a right SVC to be used in the repair of a sinus venosus atrial septal defect and the larger SVC could be used when a cavo-pulmonary shunt is to be created.

This paper presents another sign for suspecting a left superior vena cava (LSVC) at cardiac catheterization.

MATERIALS AND RESULTS

Table I records the angiographic findings in four patients in all of whom a notch was present on the inferior border of the left atrium in association with a left persistent superior vena cava draining via the coronary sinus into the right atrium. A possible embryological and anatomical mechanism for production of the atrial notch is postulated in Fig. 1.

TABLE I

ANGIOGRAPHIC FINDINGS

Case	Sex, age	Findings	Catheter passed to LSVC	Notch present on inferior border of left atrium
1	F 3.5 months Figs. 2A, 2B	Pulmonary valve stenois Pulmonary infundibular stenosis VSD Right sided aorta Left superior vena cava draining to coronary sinus	Yes	Yes
2	M 1 year 10 months Figs. 3A, 3B	Right ventricular hypertrophy Infundibular pulmonary stenosis Pulmonary valve stenosis VSD Left superior vena cava draining to coronary sinus	Yes	Yes
3	M 8 weeks Figs. 4A, 4B	Transportation of great vessels Hypoplastic stenosed mitral valve VSD Left superior vena cava draining to coronary sinus	Yes	Yes
4	F 10 years Fig. 5	Mitral regurgitation Left superior vena cava draining to coronary sinus	Yes	Yes

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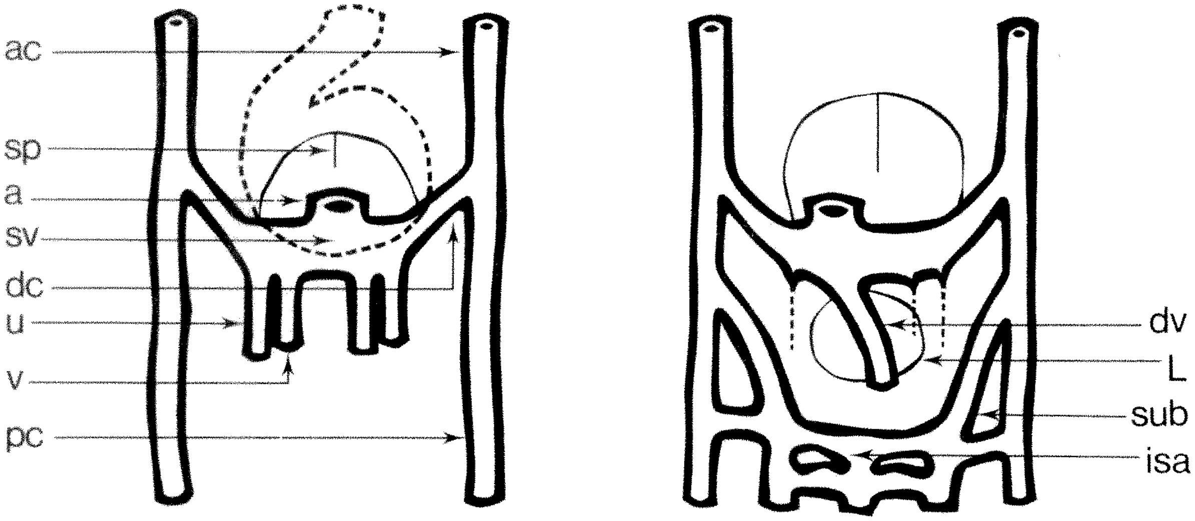
*This paper is based on an original observation by Dr. Urquhart though he did not live to see the final form of the publication. His wisdom, knowledge and expertise are greatly missed.



A.

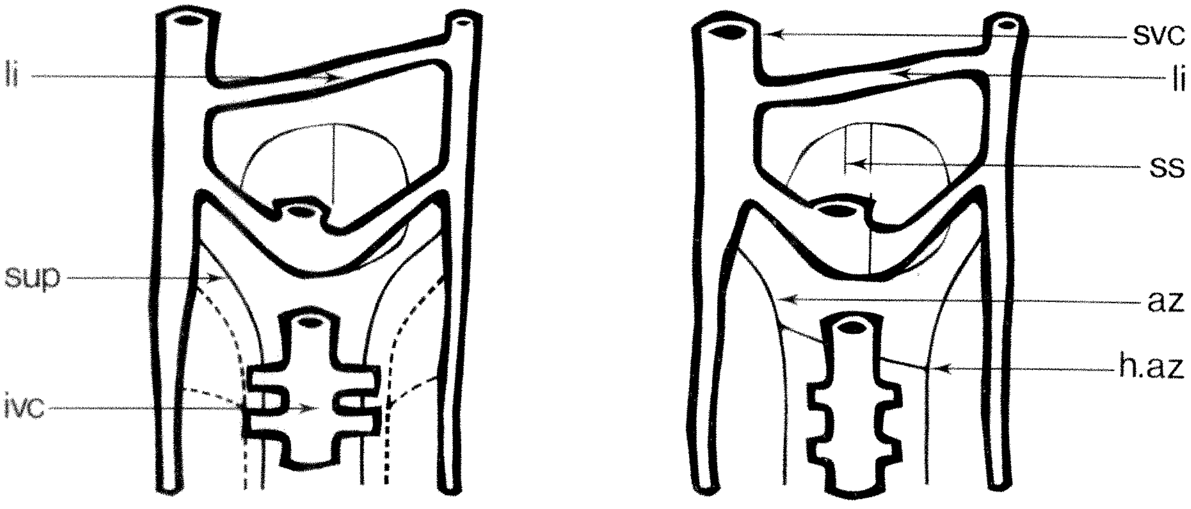
4 weeks

a – common atrium
sp – septum primum
sv – sinus venosus
dc – duct of Cuvier
u – umbilical vein
v – vitelline vein
ac – anterior cardinal vein
pc – posterior cardinal vein

B.

5½ weeks

dv – ductus venosus
L – Liver
sub – subcardinal vein
isa – intersubcardinal anastomosis



C.

6 weeks

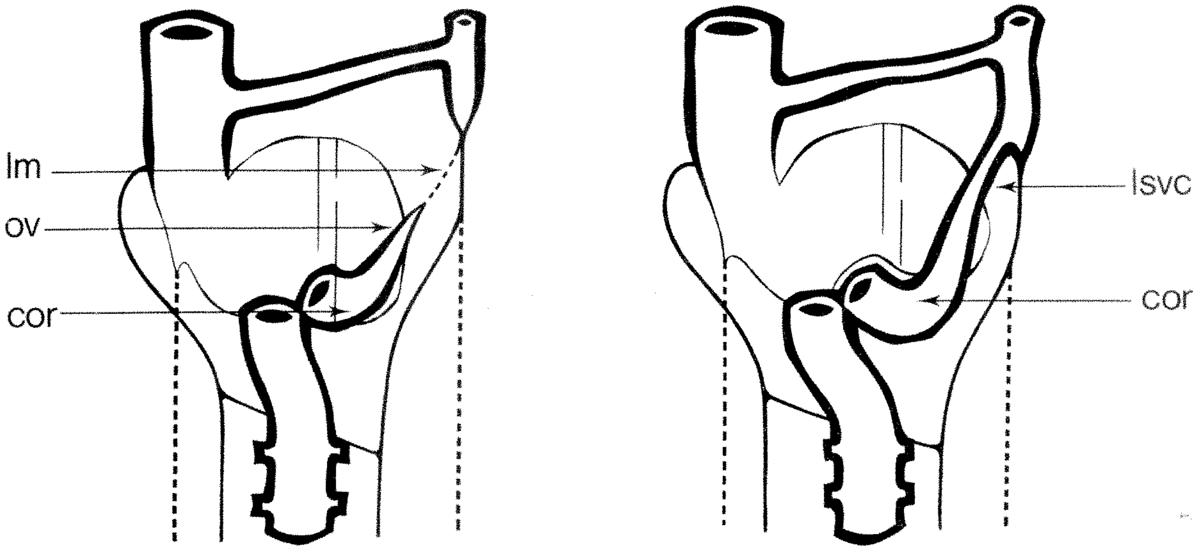
sup – supracardinal veins
ivc – inferior vena cava
li – left innominate vein

D.

7 weeks

svc – superior vena cava
li – left innominate vein
ss – septum secundum
az – azygos vein
h.az – hemi-azygos vein

FIG. 1.



E.
8 weeks
Normal anatomy

lm – ligament of Marshall
ov – oblique vein
cor – coronary sinus

F.
Persistent left superior vena cava draining into coronary sinus.

lsvc – left superior vena cava
cor – coronary sinus

FIG. 1.

The normal development of the venous system in the human embryo and a postulated mechanism for the production of the left atrial notch.

The angio-graphic appearances are illustrated in Figs. 2–5.

DISCUSSION

It is suggested (Caffey, 1973) that a left superior vena cava (LSVC) should be defined as a structure which receives the hemiazygos vein and has a communication with the coronary sinus or a communication with the left atrium when there is no coronary sinus. In the absence of these features the vein is best described as a vertical vein.

McManus (1941), cited by Gardner and Oram (1953), classifies the various types of LSVC into:

1. Persistent superior vena cava (SVC) with right SVC (bilateral SVC).
   (a) Persistent LSVC connected to the coronary sinus and either with a cross anastomosis (left innominate vein) or without this.
   (b) Persistent LSVC draining the pulmonary veins.
2. Persistent LSVC without right SVC.

A persistent LSVC has been recorded once in 350 autopsies (Keith *et al.*, 1967) but the incidence in congenital heart disease varies between 3% (Campbell and Deuchar, 1954) and 4.3% (Fraser *et al.*, 1961).

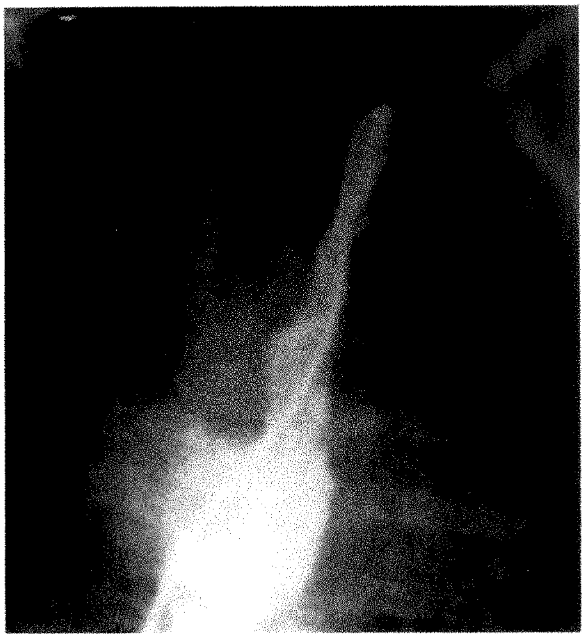
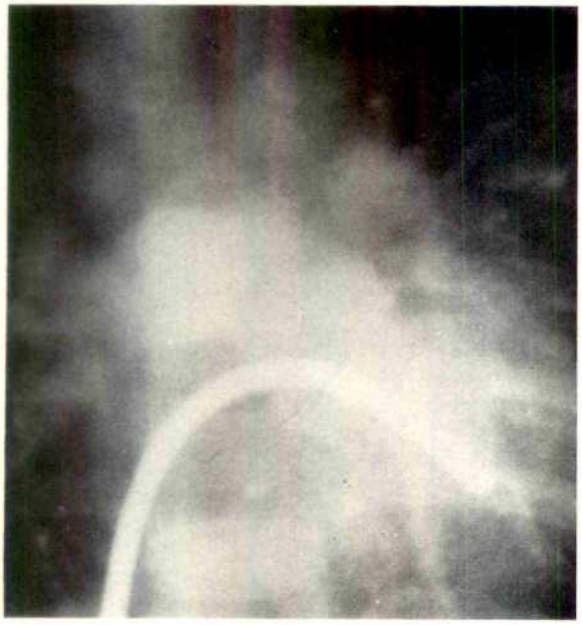


FIG. 2A. *Case 1.*

Cine. Catheter in a persistent left superior vena cava. Contrast enters right atrium.



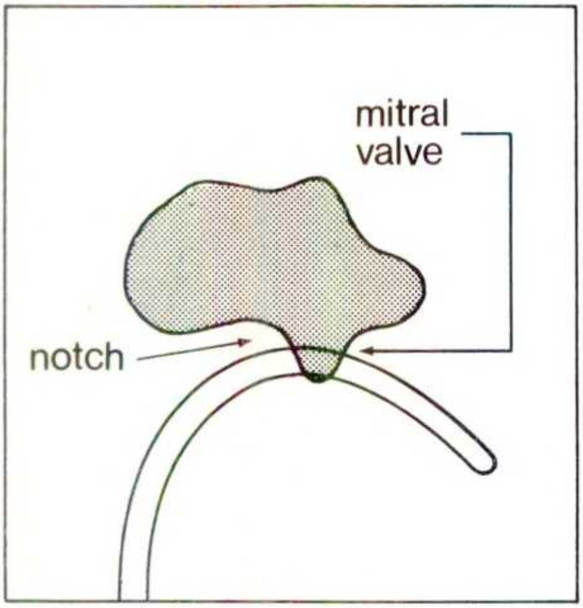


FIG. 2B. *Case 1.*

Two-plane angiogram. Late stages of a selective right ventricular angiogram showing the left atrium with a distinctive notch on the inferior border.

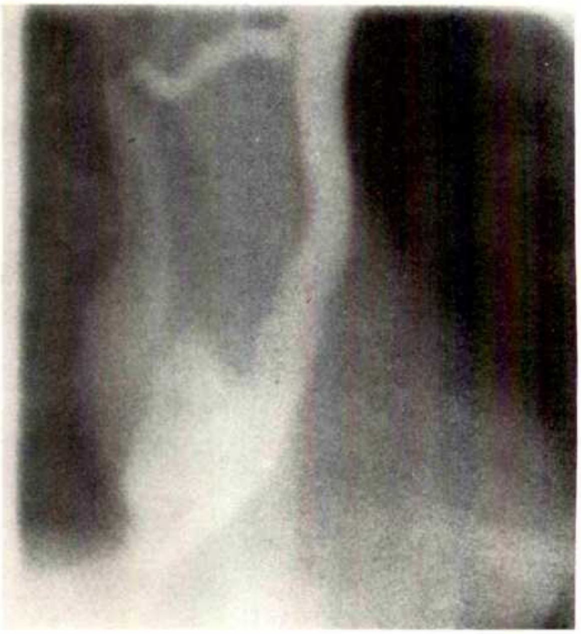


FIG. 3A. *Case 2.*

Cine. Injection into left superior vena cava. The contrast opacifies a communicating vein to the right superior vena cava. The LSVC drains to the right atrium.

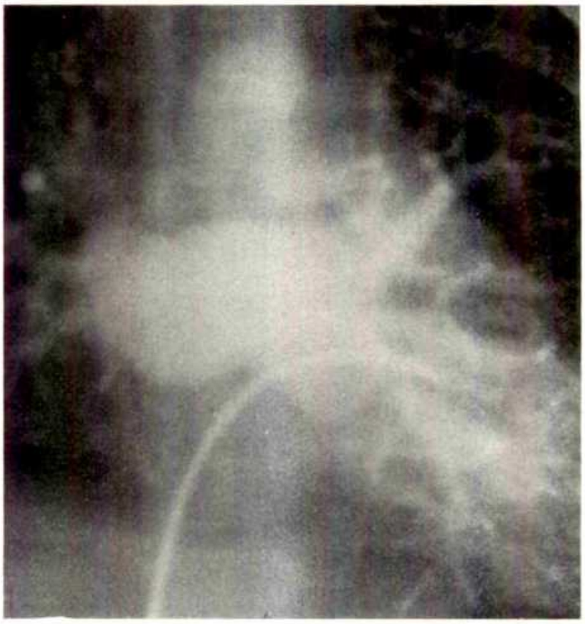


FIG. 3B. *Case 2.*

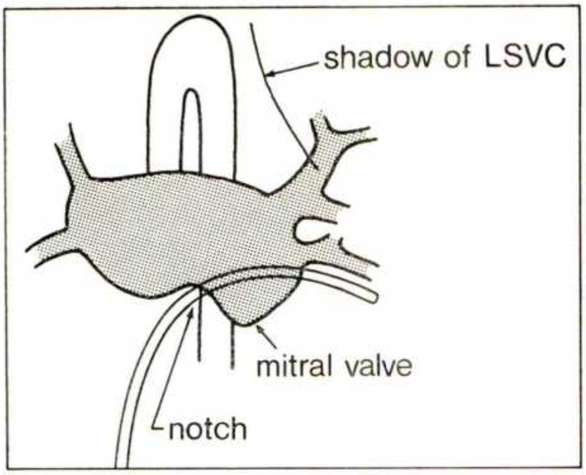
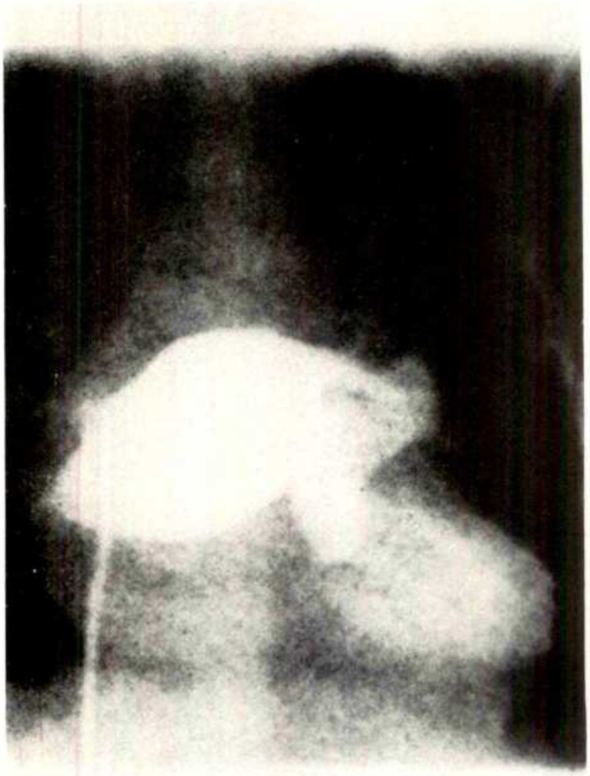


FIG. 3B. *Case 2.*
Two-plane angiogram. Late stages following right ventricular angiogram. The left atrium, left ventricle and aorta opacify. A distinct notch is seen in the inferior border of the left atrium, the mediastinal shadow is widened on the left due to the persistent left superior vena cava.



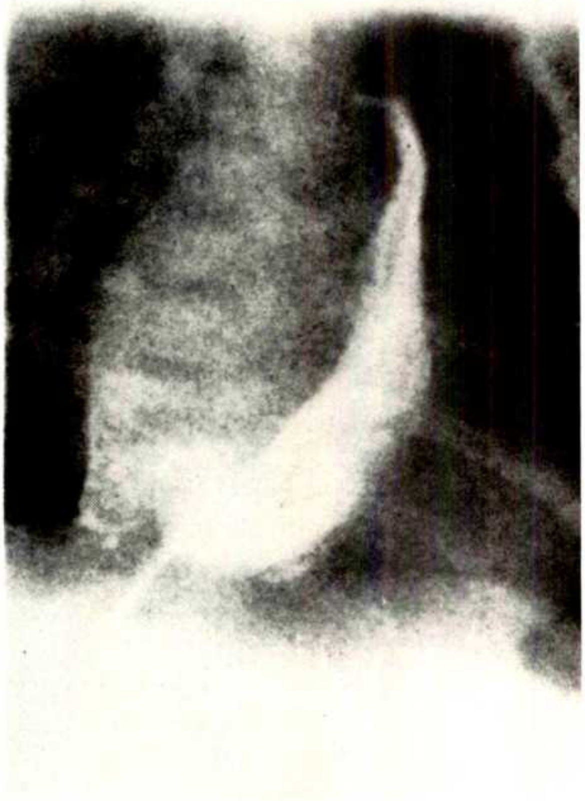


FIG. 4A. *Case 3.*
Cine. Injection into left superior vena cava which drains into the right atrium.

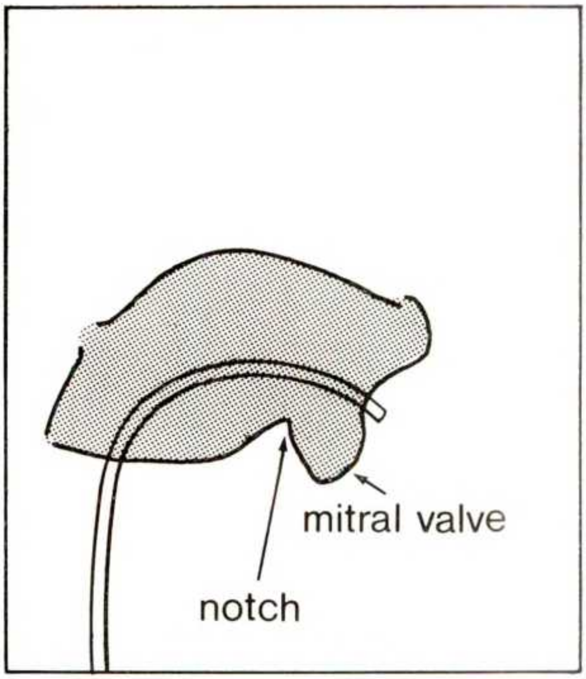


FIG. 4B. *Case 3.*
Cine. Injection into left atrium demonstrating a notch on the inferior border of the left atrium and a hypoplastic stenosed mitral valve.

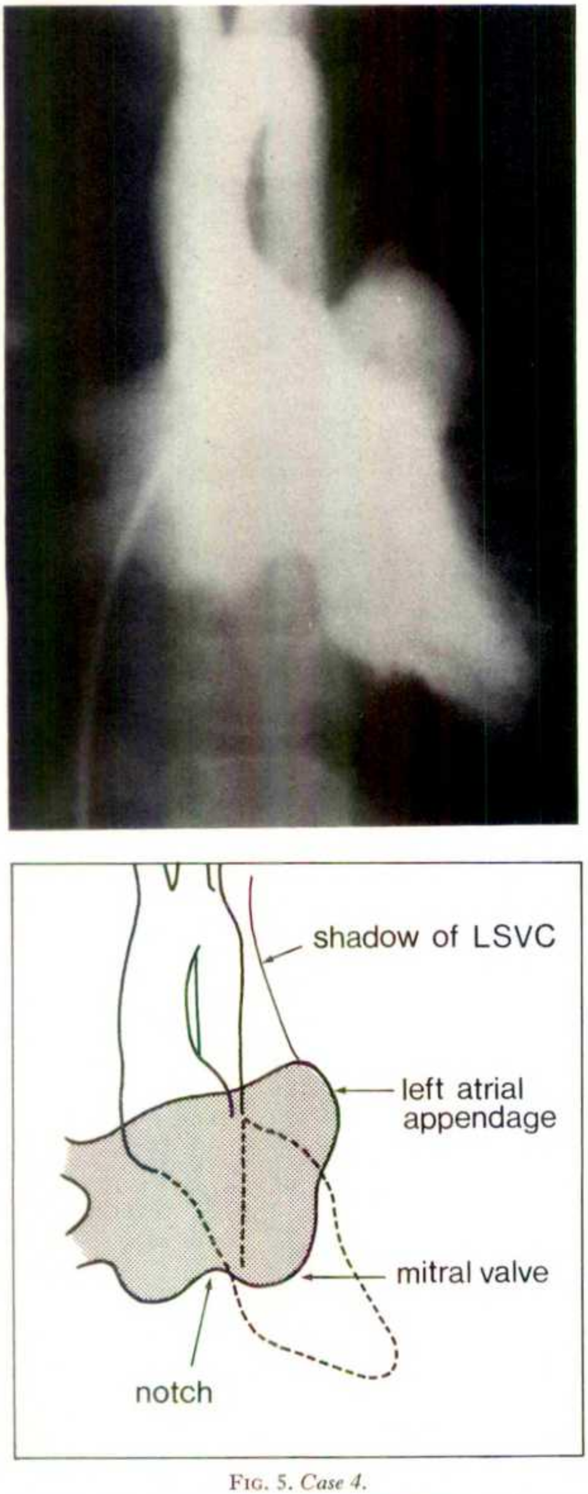


FIG. 5. *Case 4.*

Two-plane angiogram. Selective left ventricular angiogram showing mitral regurgitation, a notch on the inferior border of the left atrium and widening of the left of the mediastinum due to the persistent left superior vena cava.

LSVC may occur either as an isolated anomaly or in association with other congenital malformations such as total anomalous pulmonary venous drainage, transposition of the great arteries, ventricular septal defects and persistent ductus arteriosus. Wood (1968) records it in 5% of atrial septal defects, 22% of atrio-ventricular canal defects, and 20% of cases with Fallots tetrology. It has also been found in association with tricuspid atresia (Campbell and Deuchar, 1954), pulmonary stenosis or atresia (Campbell and Deuchar, 1954; Fraser *et al.*, 1961) and asplenia (Randall *et al.*, 1973; Snellen and Dekker, 1963).

A persistent LSVC can sometimes be identified on plain chest films as a soft tissue density in the upper left paramediastinum, though often this cannot be distinguished in young infants from a thymic shadow. At cardiac catheterization the catheter may pass into the anomalous vein and then a direct angiographic demonstration is possible (Figs. 2A, 3A, 4A). Indirect angiography by contrast injections into the left subclavian or left innominate vein is also of value.

This paper presents another sign for suspecting the presence of a left superior vena cava. It is postulated that a notch on the inferior border of the left atrium is caused by a dilated coronary sinus receiving blood directly from a persistent left superior vena cava. In the experience of one of us (W. U.) it is a constant finding in cases with a LSVC when the left atrium is normal in size, but it is less marked when there is total anomalous pulmonary venous drainage and the left atrium is small. We have not seen this angiographic change in any other clinical context nor have we seen previous reports of it in the literature.

ACKNOWLEDGMENTS

I would like to thank Mr. Lidington of the Department of Graphics at the University of Newcastle upon Tyne for the line diagrams; Dr. P. M. Hacking for his constructive comments; The Department of Photography at the University of Newcastle upon Tyne for the photographic prints and Miss Sheila Tate, Mrs. A. Hall and Mrs. M. Shepherd for valued secretarial help.

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Book reviews

Atlas of Pediatric Nuclear Medicine. By P. O. Alderson, D. L. Gilday, H. N. Wagner, Jr, 1978, pp. xv+296 (YB Medical Publishers, London), £30·50.
ISBN 0-8016-0107-X

At a time when nuclear medicine is beginning to become established in children's hospitals in this country, it is salutary to realize that this atlas is based largely on the experience of Dr. Gilday from the Hospital for Sick Children in Toronto, acquired over the past eight years. The arrival of an up-to-date text is to be welcomed as there has been no reference work on the subject published since 1974.

The layout of the book is more comprehensive than many atlases; after a short introduction, the chapters are arranged by systems, each of which begins with a detailed description of the method employed to obtain diagnostic images. This advice will be invaluable to the radiologist beginning these procedures, and will avoid the false positive errors, for instance in the diagnosis of Meckel's diverticulum, which are so damaging to the reputation of a new diagnostic facility. The chapters are then presented in the fashionable "problem-orientated" approach with good clinical detail and excellent illustrations of the appropriate X-rays and scans. Also included in the text are tables and references which are well chosen and up to 1978.

But this book is not only for the radiologist doing paediatric scanning; paediatricians would be well advised to browse through and rethink more traditional and invasive methods of investigation, and the nuclear medicine specialist will find information about unusual childhood conditions ranging from the bone scan appearance in Engelmann's disease to the diagnosis of transient myocardial ischaemia in the newborn diagnosed by ^{201}thallium scintigraphy. This atlas is recommended for your department bookshelf.

S. T. MELLER.

Diagnostic radiology in clinical medicine. By Rosalind H. Troupin, 2nd ed. 1978 pp. xiii+172. (Year Book Medical Publishers, Chicago) £9·25.
ISBN 0-8151-8851-X.

This small paperback aims to present diagnostic radiology including nuclear medicine, ultrasound and CT scanning, to clinical medical students. There are ten chapters in 154 pages on such topics as chest films, bone films, gastro-intestinal examinations, special imaging techniques, etc. and an epilogue (which consists of some answers to questions posed in the text and a bibliography surprisingly detailed for medical students). There are plenty of small, clear illustrations with some helpful diagrams and correlations of the appearances of the same lesion (*e.g.* a renal cyst) shown by differing imaging techniques.

There are brief outlines of suggested method of examination of films, followed by very concise summaries of some radiological signs and the appearances in various clinical situations. The material selected ranges from the simple (*e.g.* pneumothorax, pneumonia etc.) to the more exotic (*e.g.* bleeding from a colonic diverticulum demonstrated by arteriography).

There are plenty of Americanisms and an interesting list of "typical" changes combining technical and professional fees, for radiographic examinations in the USA.

In such a concise book much must be and is omitted. The selection of the material is obviously a matter of personal preference of the author. My general impression of the book presents a clear interesting review of radiology, integrating its various branches well. The presentation is, naturally and rightly, aimed at American students who may well find the cost is justified by the clear writing, good illustrations and comprehensive cover. Time will tell whether British students will react as favourably.

DAVID H. TRAPNELL.

1979, *British Journal of Radiology*, *52*, 862–864

A new variety of "empty sella" with cystic intrasellar dilatation of the recessus infundibuli

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(*Received January 1979 and in revised form March 1979*)

ABSTRACT

A new variety of the "empty sella" consisting of polycystic intrasellar dilatation of the infundibular recess is described. The underlying embryonal developmental anomaly of the pituitary gland and diaphragma sellae and the possible effect of increased intracranial pressure are discussed and the malformation is compared with embryonal stages of ventricular development.

Isolated intrasellar cysts (Friedmann and Marguth, 1961; Guiot *et al.*, 1971; Nadjmi, 1965; Shanklin, 1949; Schaeffer, 1924; Taveras and Wood, 1976; Weber *et al.*, 1970) as well as cisternal intrasellar herniations (Bajraktari *et al.*, 1977; Bernasconi, 1972; Busch, 1951; Calkins, 1968; Engels, 1958; Kauffmann, 1968; Kaufmann *et al.*, 1977; Lee and Adams, 1968; Peeters, 1973; Ring and Waddington, 1966; Sutton and Vezina, 1974) are well known findings which can be shown on the axial computed tomography as zones of hypodensity. However, further differentiation between intrahypophyseal cysts and arachnoidal herniations is only possible by cisternography.

A third variety of intrasellar cerebrospinal fluid containing space has been reported in two cases (Kühne and Schwartz, 1975; Cabanes, 1978) in which there was a protrusion of the third ventricle down to the hypophysis, which was confirmed by ventriculography. A comparable case is demonstrated. The underlying disorder of development and its possible relation to increased intracranial pressure are discussed.

CLINICAL FINDINGS

A female patient, 47 years old, presented with a three months history of increased intracranial pressure, occurring intermittently with signs of headache, nausea, vomiting, vertigo, combined with a progressive psycho-organic syndrome and signs of a bilateral pyramidal tract lesion.

VENTRICULOGRAPHY

After percutaneous needle trepanation (Gilsbach and Schumacher, 1978) and puncture of the anterior horn of the right ventricle ventriculography with Dimer-X revealed symmetrical hydrocephalus due to complete block of the cerebral aqueduct at the point where it leaves the third ventricle (Fig. 1). There was dilation of the infundibular recess of the third ventricle, which showed multi-cystic dilatation within the sella with a smooth surface and a basal convex margin, conforming to the configuration of the floor of the sella.

Right retrograde brachial angiography demonstrated an haemangioblastoma in the region of the left cerebellar hemisphere.

After preoperative decompression the tumour, which had the histological appearances of a capillary haemangioblastoma, was removed.

DISCUSSION

According to Faglia *et al.* (1973) and Caplan and Dobben (1969) a partly empty sella is not uncommon occurring in between 8 and 35% of the population.

Up to now, the empty sella has been shown to be due to a protrusion of the subarachnoidal space (du Boulay and Gammal, 1966; Schaeffer, 1924; Schüller, 1926; Tönnis *et al.*, 1954; Weisberg, 1975), a communicating cavity caused by rupture of a primary

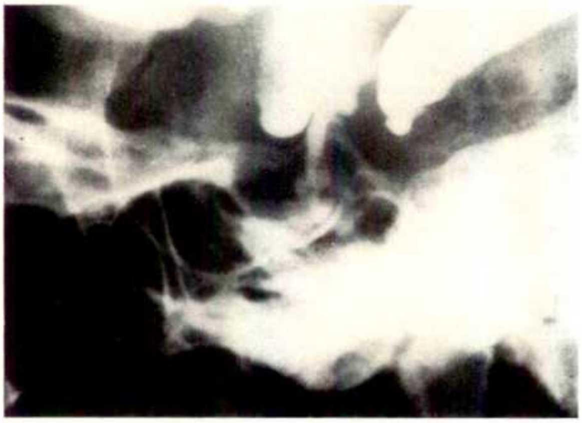

FIG. 1.

Ventriculogram. Symmetrical hydrocephalus internus as a result of complete obliteration of the cerebral aqueduct. Extended infundibular recess with polycystic distension in the sella. (Water soluble contrast medium.)

hypophyseal cyst (Busch, 1951; Weber *et al.*, 1970) or a protrusion of the basal parts of the third ventricle (Kühne and Schwartz, 1975; Cabanes, 1978). Because of the multiple vesicles at the end of the dilated infundibulum (Fig. 1) our case is considered to be a primary malformation. A possible explanation may be arrest of the obliteration of the infundibular recess (Fig. 2).

Although in our patient there was considerably raised intraventricular pressure as a result of the occlusion of the cerebral aqueduct, this is unlikely to be the sole cause of the changes, since it tends to distend especially the anterior part of the third ventricle and the optic recess (Huber and Rivoir, 1973; Twining, 1939). Corrales and Torrealba (1976) were able to show that the optic recess may dilate severely with hydrocephalus and prolapse into the sella, and that there may be ballooning of the premamillary portion of the third ventricle, but the infundibular recess remains unchanged.

The variety of the empty sella syndrome described in this paper, must be regarded as a very rare malformation. The extensive research made by Schaeffer (1924) and Bull (1956) on the basal structures of the third ventricle did not reveal an abnormality similar to that in our case. Therefore, in our opinion, the variety of "empty sella" shown in this patient was caused by a combination of increased intraventricular pressure and an underlying developmental malformation of the infundibular recess.

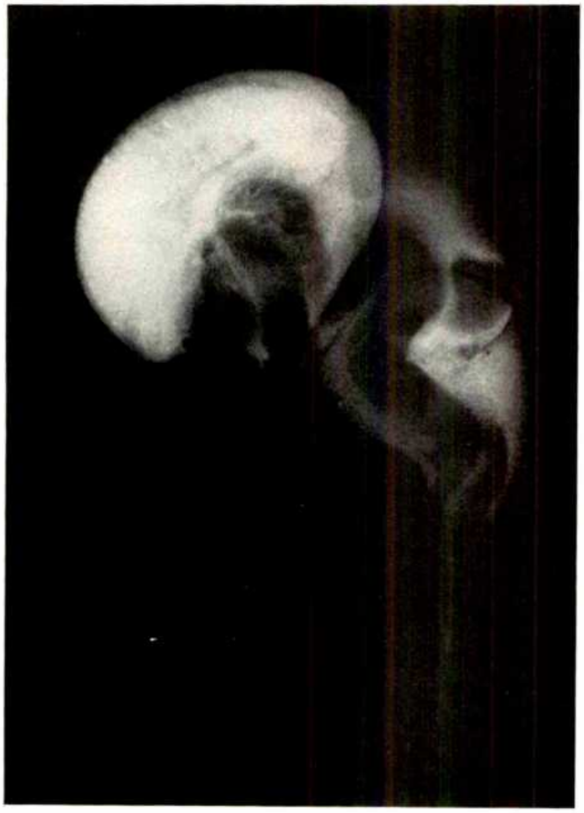

FIG. 2.

Ventriculogram. Eight weeks old human fetus (43 mm) with an infundibular recess just beginning to obliterate. ($BaSO_4$; enlargement × 3.)

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Book reviews

Nuclear medicine in clinical practice. Edited by P. B. Schneider and S. Treves, pp. xii+320, 1978 (Elsevier/North-Holland). $84.50/Dfl. 190.
ISBN 0-444-80052-2

It is a repeated refrain that there is no good book on nuclear medicine for doctors keen to study and use this discipline. A book entitled "Nuclear Medicine in Clinical Practice" surely should meet this requirement. Unfortunately again one is disappointed. The most important requirement of a good clinical text is that the discipline is described from the point of view of the ward clinician in relation to the problems that the patients present. It should not be an embellishment list of possible diagnoses in which nuclear medicine might possibly help. This book is better than some since the chapters on the lung, the blood, inflammatory lesions and peripheral vascular disease are well worth reading. So many of the other chapters are mediocre, such as those on paediatrics, the brain, the heart, the thyroid, the liver and the kidney and these do not meet the above requirement.

The patchiness of the contributions seems to correlate with the modernity of the references, some chapters have very few references more recent than 1974, in others the more recent references are only related to the authors of the chapter whereas the good chapters have references from the 1977 literature mainly American. The chapter on adrenal imaging does not mention the use of commercially available selenomethyl cholesterol with its advantages of easy storage and lack of the need for thyroid suppression. There is virtually no mention of emission tomography, of technetium labelled cholegraphic agents or of quantitative static imaging.

In conclusion as a descriptive piece of nuclear medicine the text is fair but as a tactical approach to clinical practice, it fails.

K. E. BRITTON.

Brachytherapy. By B. Pierquin, D. Chassagne, C. Chahbazian and J. F. Wilson, 1978 pp. xv+217, (Warren H. Green Incorporated, Saint-Louis, Missouri, U.S.A.) $22.50.
ISBN 0-87527-164-2

Bernard Pierquin's well-known *Précis de Curiethérapie* has been revised with the help of new authors, and translated into English under the title of *Brachytherapy*. This is defined here as radiation therapy using radioactive sources at less than 5 cm from the tumour or inside the tumour. There are short sections on the radioactive isotopes used, the principles of the techniques of insertion, after-loading and dosimetry. The rest of the book describes in more detail the application of brachytherapy at different anatomical sites.

The authors give credit to other innovators in this field, but mainly limit their descriptions to those afterloading techniques used in Villejuif and Creteil and the system of dosimetry known as the Paris system. The descriptions of the techniques are brief and may not easily be followed by those who have not seen them demonstrated. Similarly the section on dosimetry is short and densely written. There are only brief discussions of the indications for treatment, pathology and results. A more detailed analysis of the results from these centres would have been of great interest.

The quality of production of this book is poor; there are several misprints, the diagrams are poorly printed, and the translation is uneven.

This book is too brief for the newcomer to the field of interstitial radiotherapy, but it would be a useful précis for the more experienced. More detail can be obtained from the extensive reference lists, but as these are mainly in French it is to be hoped that eventually an extended description of the operative techniques, dosimetry and results will be published by these authors.

K. R. DURRANT.

1979, *British Journal of Radiology*, 52, 865–869 NOVMEBER 1979

Ossification of the posterior longitudinal ligament of the spine

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ABSTRACT

"The Japanese disease" or ossification of the posterior longitudinal ligament of the cervical spine was initially thought to affect only the Japanese people. Non-Japanese Asian and Caucasian cases have been reported but appear to be exceedingly rare. The reason is unknown. Although the disease appears to be generally benign, it can cause a myelopathy. We present here 16 non-Japanese patients in Singapore who were found to have ossification of the posterior longitudinal ligament in the cervical, thoracic and lumbar spine.

In 1960, Tsukimoto presented an autopsy report of a 47-year-old man with progressive myelopathy caused by an ossified posterior longitudinal ligament extending from the third to the fourth cervical vertebra. This account was soon followed by several other Japanese reports of ossification of the posterior longitudinal ligament of the cervical spine in Japanese patients. These individuals were either asymptomatic or had symptoms of cervical spondylosis. A few presented with a cervical myelopathy.

Terayama *et al.* (1964), introduced the term "ossification of the posterior longitudinal ligament of the cervical spine" to differentiate this condition from ankylosing spondylitis, senile ankylosing hyperostosis (Forestier and Rotes Querol's disease) and spondylosis of the spine. Autopsy and biopsy reports confirm the pathological change to range from unorganized calcification to true bone formation (Furuya *et al.*, 1968; Onyi *et al.*, 1967; Palacios *et al.*, 1971). Ossification in the thoracic and lumbar regions was also found but is much less common.

The disease appeared to be confined to the Japanese until 1969 when Minagi and Gronner (1969) reported the first two caucasian cases in the United States. Further reports added another ten caucasian and one Negro patient (Bakay *et al.*, 1970; Breidahl, 1969; Forcer and Horsey, 1970; Palacios *et al.*, 1971). The only report of non-Japanese Asians affected with this disease came from Soo and Sachdev (1971) who described two patients from Malaysia. We present here 16 non-Japanese Asians from Singapore with ossification of the posterior longitudinal ligament in the cervical, thoracic and lumbar spine.

PATIENTS

There were 16 patients with ossification of the posterior longitudinal ligament, with equal sex incidence. Their ages ranged from 45 to 79 years. Ten were Chinese, four Indian and two Malay. Singapore's ethnic distribution is 76% Chinese, 15% Malay, 7% Indian and 2% of mixed origin.

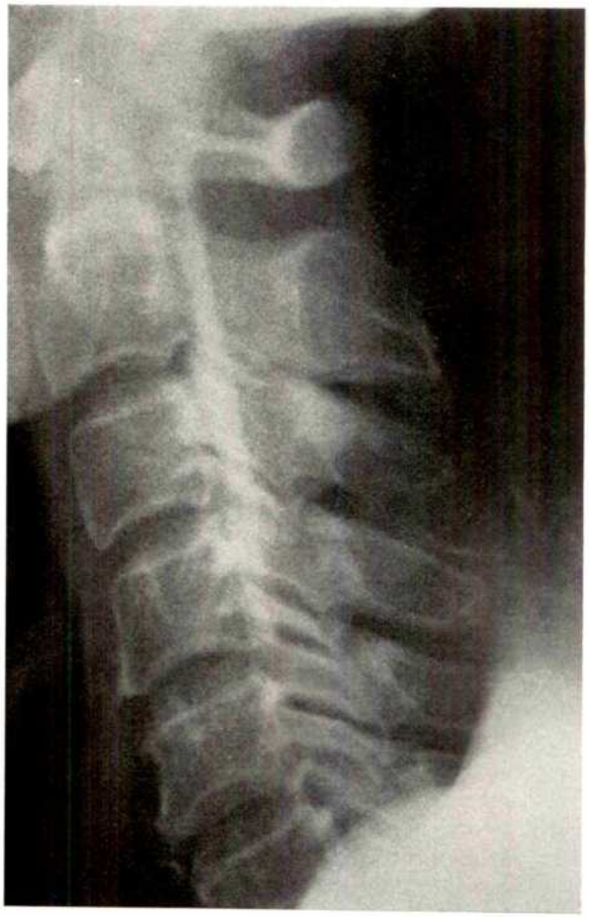

FIG. 1. *Case 10.*

Typical example of marked ossification of the posterior longitudinal ligament of the cervical spine extending uninterruptedly from C2 to C4.

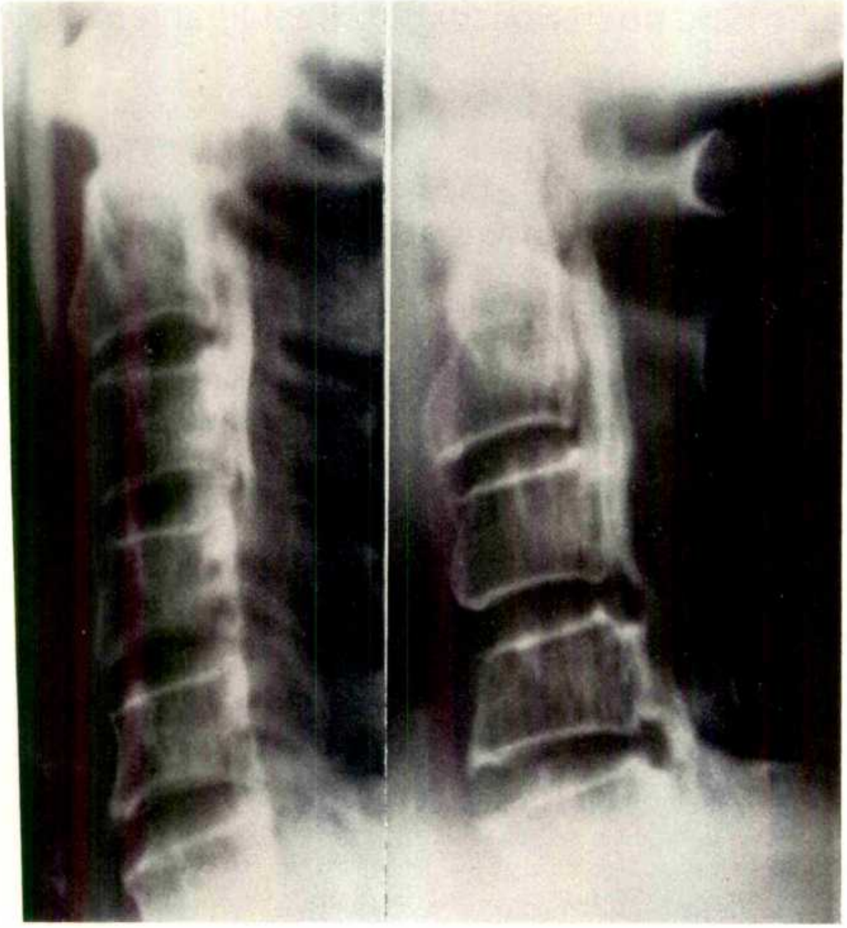

FIG. 2.

Lateral tomograms of Case 1 and 3, showing C2 to C3 ossification, with sagittal thickness varying from 1 to 3 mm.

The patient who had the thickest ossification presented with a left cervical radiculomyelopathy. Eleven others suffered symptoms consistent with minor spondylosis and the remaining four were incidentally detected. Those with symptoms responded favourably to conservative treatment.

There was predilection for the cervical spine. Twelve patients had purely cervical ossification (Figs. 1, 2, 3 and 4). One had both cervical and thoracic (Fig. 5), one cervical and thoraco-lumbar, one thoracic and lumbar (Fig. 6) and one only at the thoraco-lumbar junction (Fig. 6). The sagittal thickness of the ossification varied from 1 to 8 mm. The length of ossification was also variable. Ossification in the thoracic and lumbar spine tends to be interrupted and occurred mainly over the disc spaces (Fig. 6). Minor to moderate spondylotic changes were seen in all patients with cervical ossification but these corresponded poorly with the site of the ossification. It was observed that six of the 14 cervical cases also had calcification of the nuchal ligament at the C3–C5 level. However, this is considered not significant as a random sampling of the cervical spine of 100 patients over the age of 40 years, revealed an incidence of 32% calcification of the nuchal ligament.

DISCUSSION

The posterior longitudinal spinal ligament extends within the spinal canal from the body of the axis vertebra to the sacrum. Ossification or calcification of this ligament, as an isolated phenomenon, is obviously very rare in non-Japanese people compared to an incidence of 0.7% to 1.7% in Japanese patients presenting with cervical disorders (Nagashima, 1972; Onyi *et al.*, 1967). Our paper suggests a very low incidence among Asians in Singapore and the

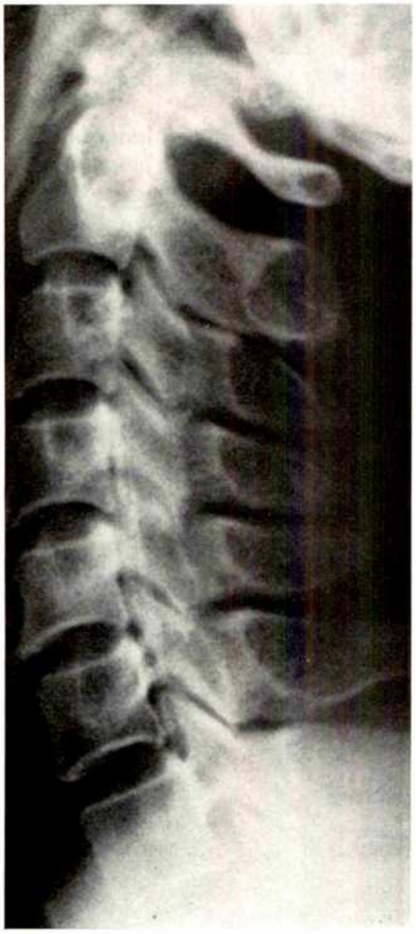

FIG. 3. *Case 6.*
Ossification occurring in the mid-cervical spine (C4–C6) and showing a stratified appearance.

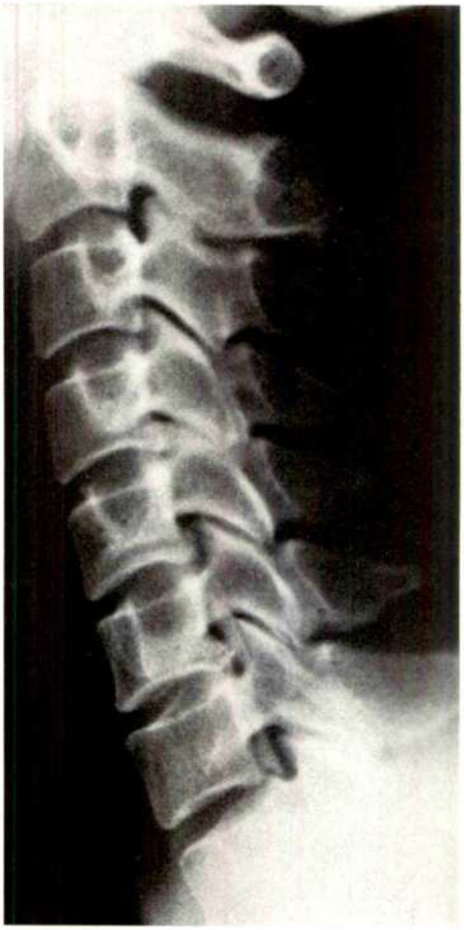

FIG. 4. *Case 7.*
Ossification at C6 and C7 level with a gap over the C6–7 disc space.

distribution corresponds with the ethnic composition. This impression is supported by Soo and Sachdev (1971) from Malaysia who found two patients on reviewing 96 symptomatic and 160 asymptomatic patients.

Ossification of the posterior longitudinal ligament occurs predominantly in the cervical spine. It can range from C2 to C7 but is seen most often between C2 and C4. The length of the ossification varies from one to several vertebral bodies and may be broken at the disc levels. The sagittal thickness varies from 1 to 8 mm. While the disease shows a predilection for the cervical spine, it can occur in the thoracic and lumbar spine. The pattern of ossification in our cases is similar to that of other reports (Forcer and Horsey, 1970; Hiramatsu and Nobechi, 1971).

Patients are in the late middle to old age group. There is no sex predilection, no familial tendency and no association with any systemic disease. Calcification in this site has been described in flurosis (Singh *et al.*, 1962) but the phenomenon is invariably accompanied by calcification or hyperostosis at other sites and there are usually clinical signs of the condition. In the present cases, laboratory investigations were all normal and there was no clinical evidence to suggest fluorosis. The ossification appears independent of the degree and site of spondylosis (Nagashima, 1972). Clinically, it may be asymptomatic or present as a neurological disorder. Symptoms are usually minor but may be severe when there is spinal cord compression. Those with a myleopathy will show partial or complete myelographic blocks

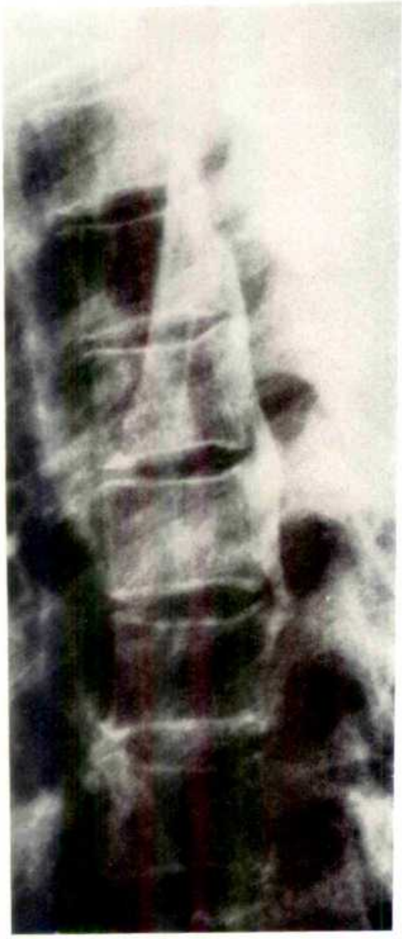

FIG. 5. *Case 11.*
Ossification of the posterior longitudinal ligament in the upper thoracic spine.

and usually respond favourably to decompressive laminectomy (Onyi *et al.*, 1967).

The aetiology is unknown. A degenerative cause is most likely and there is some histological evidence to suggest that intervertebral disc degeneration could be the primary lesion (Furuy
et al., 1964; Tsukimoto, 19
acute herniated intervertebr
(Palacios *et al.*, 1971).

Ossification of the poste
is, therefore, not an exclu
unless its occurrence is being ove
rarity in other ethnic groups is interesting importance of the disease lies in the fact that, although it appears to be part of the degenerative process and is usually benign, it may cause severe myelopathy requiring spinal decompression.

ACKNOWLEDGMENT

Thanks to Dr. F. C. Ng, Tan Tock Seng Hospital, Singapore, for cases 11 and 12.

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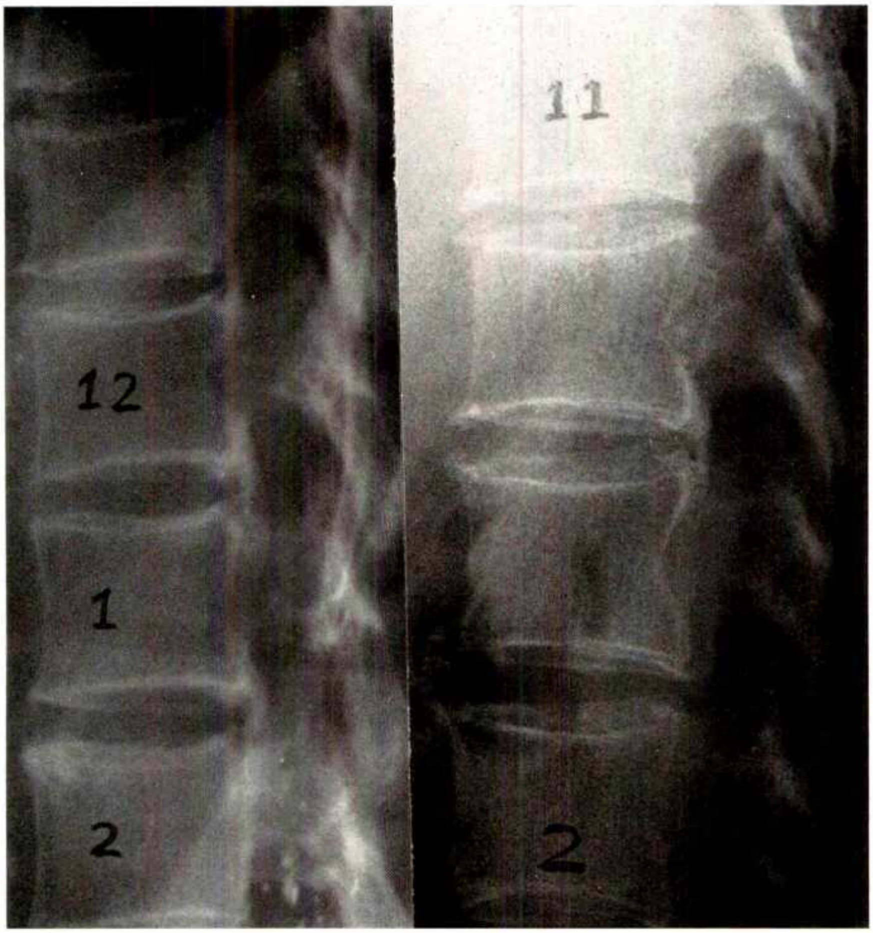

FIG. 6. *Cases 12 and 14.*
Lumbar ossification occurring mainly at the level of the disc spaces.

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Age related gross changes of the liver and right diaphragm, with special reference to partial eventration

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ABSTRACT

A total of 38937 6×6 cm chest films, made in three series of check-up programmes for local residents above the age for nursery school, were examined for partial eventration of the right dome of the diaphragm in relation to age. It was found that after nursery school age, eventration and irregularity of the right dome increased with age, particularly among women over the age of 60. In a series observed in a rural region, marked eventration was found in more than 1% of the women above 60 years. In another study on 1 332 liver scans in patients without intrinsic liver disease, a prominent, dome-like elevation of the right lobe of the liver was also very frequent among older women. It is concluded that the majority of right-sided eventrations are aquired and may be attributable to dietary and dressing habits.

The superior surface of the liver is in direct contact with the right dome of the diaphragm and the curvature of the right dome seen in the chest film should closely reflect the liver surface.

There has, however, been no thorough study of this relationship. Radiological changes in the contour of the right dome is usually discussed in its relation to pleuropulmonary diseases (Felson, 1973).

In the course of our study of gross changes of the liver, it became clear that partial eventration of the right side is more frequent among older women. Some of the extreme cases had been mistaken for an intrathoracic mass (Okuda and Shimokawa, 1972).

MATERIALS AND METHODS

A total of 38937 6×6 cm PA chest films were studied. They had been made during a mass physical check-up programme for the residents and school children of a rural area of Sambu-gun, Chiba Prefecture. The rolls of films were read independently by three of the authors, and those with apparent gross changes of the right diaphragmatic leaf in the absence of intrathoracic and pulmonary lesions were extracted and graded.

The changes or protrusions of the right dome were graded as follows: (+)—elevation of the right dome on the PA film above the assumed normal line of curvature by a distance of more than half but less than one intercostal space (Fig. 1), (++)—elevation above the assumed normal line of curvature by more than one but less than two interspaces; (+++)—elevation greater than two interspaces (Fig. 2).

The records of patients who had in the past two years ^{198}Au colloid or ^{99}Tc^{m}-phytate liver scan were reviewed. There were 1 332 such cases without a disease likely to lead to a gross change in the liver. The majority of these scans had been made in a search for metastases, for subtraction in pancreatic scanning, or in the differential diagnosis of hepatitis. Only the anterior scans were reviewed, and those with a prominent dome (DeLand and Wagner, 1972; Okuda and Iio, 1976) were studied further in the right lateral view and by chest X-rays. A "prominent dome" has been defined in this study as a superiorly displaced right lobe of the liver with a notch along the cranial liver border (Fig. 3).

For elucidation of the gross anatomical relationships between the liver and diaphragm, 35 cadavers from the Homes for Aged were studied. There was one female cadaver with right diaphragmatic eventration and three marked grooves and bosses of the liver surface.

RESULTS

Types of right diaphragmatic eventration

There were two cases of total eventration of the right dome of the diaphragm in the "check-up" study, but they were not included in the analysis. In others with a prominent protrusion along the curvature of the right dome, only the portion of the right dome in contact with the liver was elevated. When more than two thirds of the medial portion of the right dome was elevated, differentiation from total eventration was difficult on the anterior view alone, unless the costophrenic angle was demonstrable in its normal position (Fig. 2). In total eventration, the right dome of the diaphragm was flatter with a high position of the outer part of the dome, and on the lateral view, the entire dome was elevated. This was in contrast to partial eventration in which only the liver portion was elevated (Fig. 4). Much less frequently, only a small area of the right dome was elevated containing a small portion of the liver as in

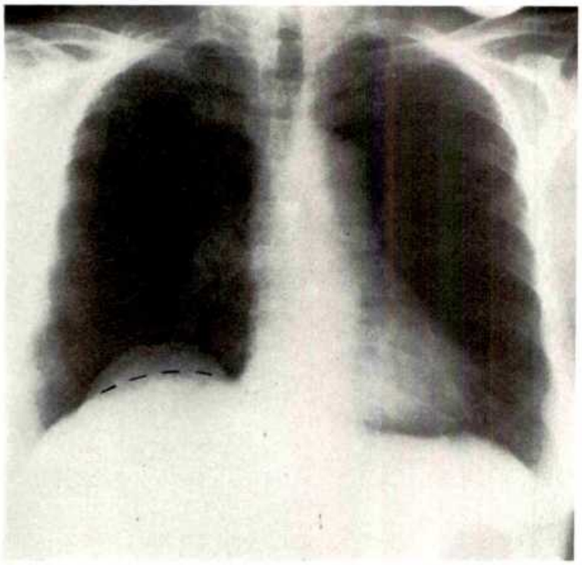

FIG. 1.

Mild (+) eventration. A portion of the diaphragm is elevated above the assumed normal level of the diaphragm by a distance of half to one intercostal space measured in the back of the patient.

Fig. 5; this segmental eventration was seen in only five cases with (++) and (+++) changes.

Incidence of eventration in relation to age and sex

The chest films in a series of 6013 residents of a rural area were reviewed. The incidence of eventration of the right dome was 0.2% in the 40 year age group, 0.9% in the 50 year age group, 2.3% in

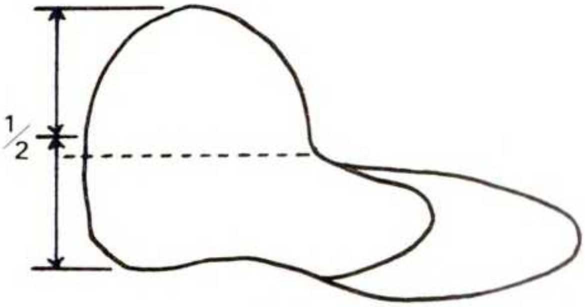

FIG. 3.

Schematic representation of the "prominent dome" in which an apparent notch or transition from the left to the right lobe along the cranial outline occurs at a level below the mid-point between the vertex and bottom of the right lobe.

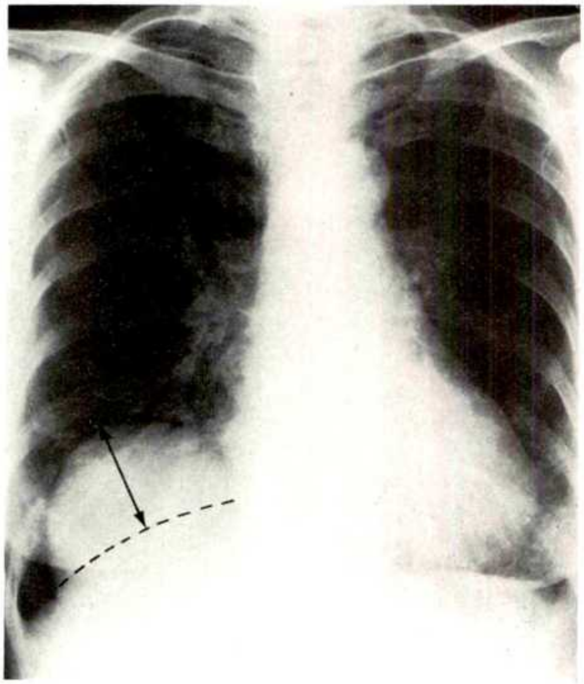

FIG. 2.

Marked (+++) eventration. A portion of the diaphragm is elevated above the assumed normal level of the diaphragm by a distance of more than two interspaces.

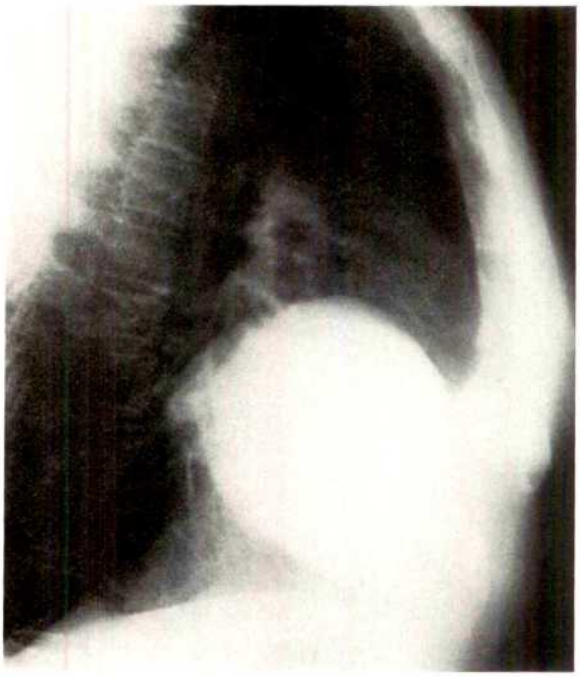

FIG. 4.

In this 67-year-old woman in whom pneumoperitoneum was necessary to differentiate between eventration and tumour the lateral view demonstrates displacement of the liver with the portion of the diaphragm covering it. The entire dome is elevated in total eventration.

the 60 year age group and 5.5% in the 70 year age group. Eventration was not seen below 40 years of age.

There was a large sex difference. The overall incidence of (+++) changes was 0.34% in the female in contrast to 0.04% in the male, and that of (+) to (++) changes, 1.53% and 0.18%, respectively.

In another series, chest films of 22425 children and nursing students were studied in comparison with 10499 adults. None of the children or students showed eventration of the right dome, whereas five adults had a (+++) eventration.

Wavy irregularities and the liver surface

The right dome of the diaphragm was often irregular in adults without evidence of pleurodiaphragmatic adhesion. Figure 6 shows one such case of wavy irregularity or (+) eventration in which pneumoperitoneum demonstrated alterations of the right dome closely related to the irregular surface of the liver. Since there is no interposing tissue between the diaphragm and liver, smooth irregularities of the right dome on a film made in deep inspiration should represent corresponding

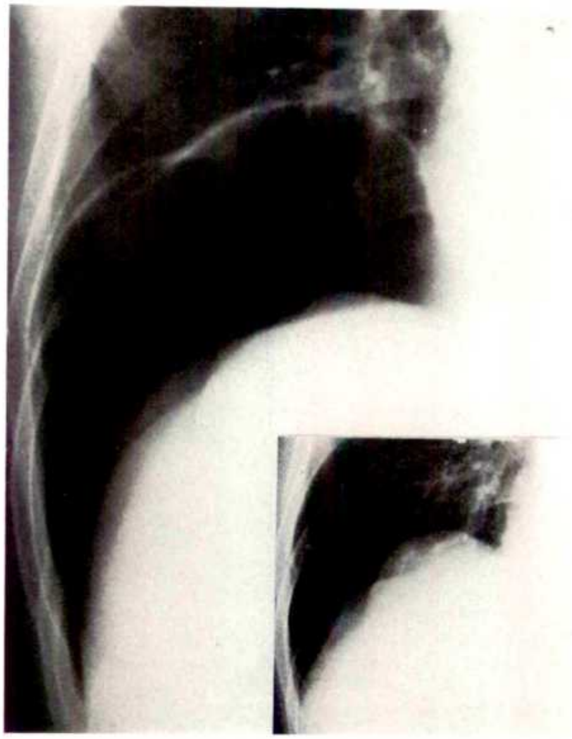

Fig. 6.

That the wavy irregularity of the right dome (insert) reflects the bosses and grooves of the liver surface is evident in the film of pneumoperitoneum.

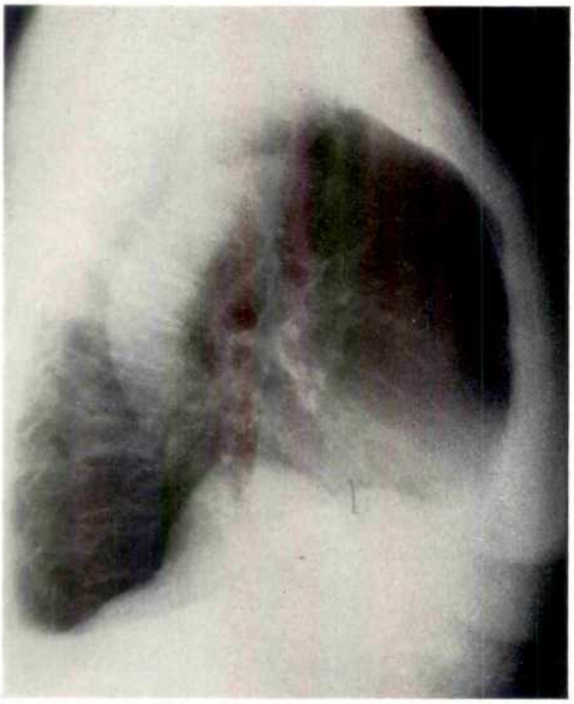

Fig. 5.

A segmental eventration in the lateral posterior portion of the right dome. A localized weakness of the diaphragm is to be suspected.

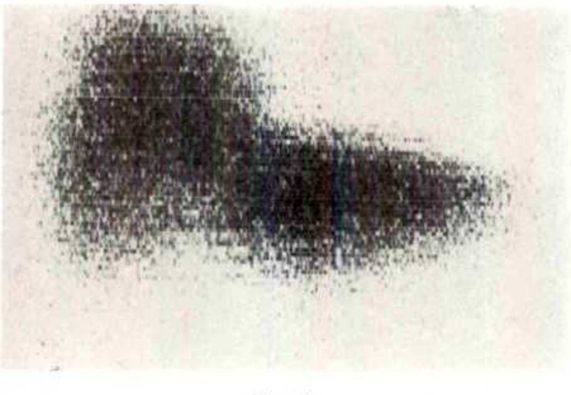

Fig. 7.

A prominent dome with a notch along the cranial border of the liver between the right and left lobes. The caudal end of the right lobe is elevated and more or less horizontal. The left lobe is relatively large suggesting that eventration is not of an extreme grade.

liver surface irregularities. Whereas none of the children showed wavy irregularities, ten of the 1645 high school students and many of the adults had wavy irregularities.

Incidence of a prominent dome and characteristics of partial eventration on the liver scan

Liver scans in 1332 patients without gross liver lesions were reviewed. There were 36 scans fulfilling the criteria for a "prominent dome". The prominent dome became more frequent with age, none being seen below the age of 30, and being more frequent among females. Of the 36, chest films were available in 21; two were interpreted as total eventration, 11 were graded as (+++) partial eventration and the remainder (++). Although liver configuration varied somewhat from case to case, particularly in the right lateral view, the following characteristics were frequently noted: (1) elevation or flattening of the caudal border of the right lobe of the liver (Fig. 7), (2) relative symmetry of the shape of the dome (Fig. 8), and (3) elevation of the anterior portion of the liver and disappearance of the antero-inferior portion of the liver in the right lateral view (Fig. 9). The study of the cadaver with typical

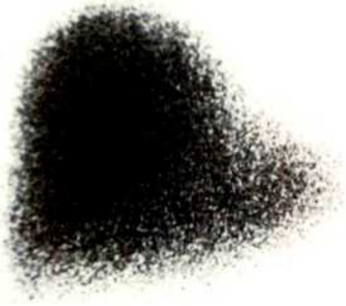

FIG. 8.

The prominent dome is more or less symmetrical with respect to a semivertical line dividing the right lobe. Since the left dome is small, part of it may be cranially dislocated together with the right lobe.

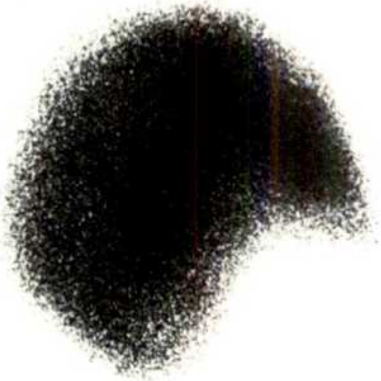

FIG. 9.

A typical right lateral view of partial eventration in which mainly the anterior portion of the right lobe has been dislocated. This finding is not necessarily specific for eventration, however, and may be misinterpreted as a defect.

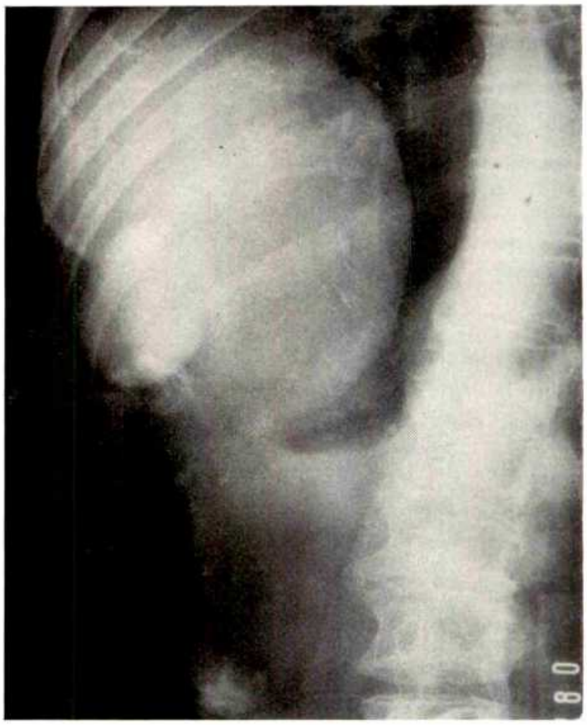

FIG. 10.

The position of the liver and gall-bladder in marked partial eventration as seen in the second oblique projection.

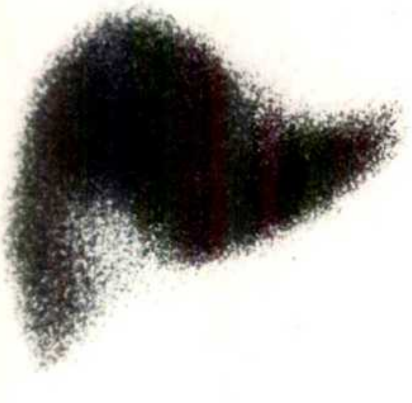

Fig. 11.

The right lobe is twisted by eventration, and the dislocated gall-bladder bed gives an area of reduced activity.

eventration demonstrated cranial displacement of the anterior portion of the liver which would account for the changes in the right lateral scan. Thus, the gall-bladder appears displaced as in Fig. 10, and on the scan the indentation due to the gall-bladder may be exaggerated and misinterpreted as a space occupying lesion (Fig. 11). The notch between the right and left lobes has also been mistaken for a defect in several cases.

Discussion

Eventration of the diaphragm is generally defined as an abnormal elevation of all or a portion of one diaphragmatic leaf (Bisgard, 1947; Larson and Evans, 1963). It may be congenital or acquired. Although hernia and eventration are different by definition (Kirklin and Hodgson, 1947), differentiation is often difficult unless an anatomical study is available (Marks, 1937). Most previous statistics have indicated that eventration is a relatively rare condition (Reed and Borden, 1935). It has been found on routine chest X-rays from one in 1400 to one in 13000; it is encountered twice as frequently in men as in women and approximately nine times more frequently on the left side than on the right (Chin and Lynn, 1956; Christensen, 1959; Kinzer and Cook, 1935; Michelson, 1961; Shah-Mirany *et al.*, 1968). The incidence of right sided eventration in the current study was much higher, especially in older women. Both hernia and eventration can be symptomatic, requiring surgery (Biscard, 1947; Chin and Lynn, 1956; Michelson, 1961; Ravitch and Handelsman, 1952). They can also be mistaken for an intrathoracic mass (Christensen, 1959; Wolfson and Goldman, 1948). In fact, needle biopsy had been done on one patient in our series before referral, and in another a pneumoperitoneum was required for differential diagnosis. A liver scan is helpful in demonstrating the intrathoracic mass to be liver (Gonzalez, 1971), but interpretation of the scan may also be a problem as in Fig. 11.

Except for congenital hernia and eventration (Bishop and Koop, 1958; Swoboda and Wolf, 1954), little information is available regarding the frequency of eventration in relation to age. The present investigation clearly demonstrated an age-related increase in the incidence of right-sided diaphragmatic eventration particularly after the age of 60 years. Although congenital eventration could not totally be excluded in individual cases, the large majority of the observed cases were thought to be acquired because of the relationship of incidence to age. The known causes of acquired eventration are phrenic nerve injury and involvement of the diaphragmatic musculature (Christensen, 1959, Clearfield, 1976; Michelson, 1961; Shah-Mirany *et al.*, 1968). Intrathoracic and pulmonary lesions could not account for the marked sex difference demonstrated in the current study. It seems more likely that the partial eventration seen in routine chest films is associated with an incomplete defect or a weakness of the right dome. Such weakness would be exaggerated if the general nutritional status was poor. Many old women living in farming areas eat poorly and wear traditional kimonos and a thick belt. Osteoporotic kyphosis is common among them. If the respiratory descent of the liver was prevented by the tight sash belt worn round the lower chest, the right dome would be stretched by the liver surface on deep inspiration; with time, the central tendon of the right dome and nearby muscle could be stretched allowing the underlying part of the liver to protrude into the thorax.

The development of diaphragmatic grooves, bosses and humps shares the same mechanism as the "corset" liver (Clearfield, 1976). Christie (1951) found diaphragmatic grooves, bosses and humps in 11.9% of 900 consecutive necropsy specimens, and the grooves were deeper in the older age groups. It seems that several bosses with regularly spaced grooves on the AP surface of the liver are a result of intra-abdominal pressure upon the liver and not due to diaphragmatic weakness, whereas the eventration producing a round, dome-like protrusion is more related to diaphragmatic weakness. The central tendon is weak compared to the surrounding muscular portion of the diaphragm; greater pressure upon the liver by the muscular portion in a ring fashion would produce a dome-like protrusion of the liver in the central area.

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Book review

Atlas of Roentgenographic Measurement. 4th Edition. By Lee B. Lusted and Theodore E. Keats, pp. xiii+354, illus., 1978 (Year Book Medical Publishers, Inc., Chicago/London), £31·00.
ISBN 0-8151-5655-3.

This is the fourth edition of a marvellous book—I well recall how my heart leapt when I discovered it as a trainee. The new reader need just be told that all the measurements he has ever tried to remember are here. They are easy to find and explained by good diagrams. The expert will inevitably detect some omissions. Perhaps the best service he can render is to point to now best forgotten measurements: my own unfavourite is the page on urethrovesical angles in stress incontinence.

For the devotee the main interest will lie in the new points made in this edition. They are discussed in an interesting preface. An attempt has been made to include new measurements from several countries around the world, for instance, highly relevant material on the normal adult nasopharynx in the Chinese. Where a new technique has arrived to help, old and new are given in sequence. Thus, radiographic and ultrasound estimates of fetal maturity are juxtaposed in the last chapter. The pancreas is looked at by endoscopic, ultrasound and CT standards. The authors discuss the problem of the varying presentations of image size between such techniques. The argument that anatomic measurements should be presented as ratio relationships is attractive. Absolute standards are valid only within the population on which they are established. Measuring norms of an organ in proportion to the individual's whole body is more useful. Body surface area is one good but perhaps forbidding reference: the authors point out that pocket calculators have made its calculation from weight (with or without height) a simple matter.

This is a book to have at the ready in everyday film reporting. It illustrates a very cheering maxim: it is not important to remember numerous facts, only where to look them up. Buy it if you can.

THOMAS SHERWOOD.

1979, *British Journal of Radiology*, 52, 876–879

Acute pulmonary distress following high-dose irradiation of the upper half of the body

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(Received February 1979 and in revised form April 1979)

ABSTRACT

Two cases of acute pulmonary distress following very shortly after irradiation of the upper half of the body are described. The first occurred one hour and forty minutes after irradiation and led to the patient's death three hours after irradiation. The second occurred 15 minutes after irradiation and was successfully treated with hydrocortisone and Frusemide. The features are the sudden onset of dyspnoea and cyanosis associated with pyrexia. Auscultatory evidence of pulmonary oedema was not apparent initially. The response to steroid alone is transitory.

High single-dose pulmonary irradiation causes transudation of extracellular fluid and diapedesis of red cells from the alveolar capillaries. The supervention of these effects on severely compromised pulmonary function can well prove dangerous.

Acute radiation pneumonitis occurring 1–16 weeks after high-dose irradiation to the whole lungs has been described by many authors. Engelstadt (1940) described his findings in rabbits, concluding that there were four stages in the development of radiation pneumonitis. Stage one started one to two hours after a large dose of radiation and lasted 24 to 48 hours. The features were degeneration of the lymph follicles and hyperaemia of the bronchial mucosa associated with increased transudation and a moderate leucocytic infiltration. Bronchial secretions also increased. Stage two he observed to be a period of relatively normal structure and function lasting two to three weeks. The third stage was principally degenerative with associated inflammation and occured 12–16 weeks after radiation. This inflammation after high doses could be severe, even fulminant, leading to rapid death. Gradually leucocytic infiltration diminished and large numbers of macrophages and giant cells were seen. The final stage was regeneration with proliferation of connective tissue and sclerosis. Bone production was even seen on some occasions. This occurred six to twelve months after irradiation.

In patients, two overt stages have been described by Warren and Spencer (1940) and Stone *et al.* (1956) and consist of an early degenerative phase and a late regenerative phase. The symptoms and signs of the degenerative phase are those of acute radiation pneumonitis. Mild cases may only suffer dyspnoea and cough. In the most severe cases fever is associated with orthopnoea and cyanosis, and death may occur, The chest radiographs show two main features, irregular widening of the mediastinum and diffuse infiltration of the affected segments of the lungs. Six to twelve months after radiotherapy fibrosis starts to develop in the affected segments. In severe cases the patient may become dyspnoeic and develop a cough. Infection may lead to death. Generally, a dose of 20 Gy (2000 rad) given to the whole lung volume in a number of fractions over 12 days should not be exceeded.

CASE REPORTS

Some cases of malignant disease of the bronchus seen in the department have been treated with upper half-body radiation as described by Fitzpatrick *et al.* (1976). This has been used both as an initial treatment to the primary and in the hope of delaying the onset of metastases. In the latter case the lower half of the body has also been treated after a six-week interval.

The irradiation was given using 8 MV X rays generated by an SL 75 linear accelerator through parallel-opposed 30×30 cm fields. The patients were treated on both their right and left sides. The dose delivered to the mid-plane of the chest was 8 Gy (800 rad). The calculated dose to the mid-point of the lungs (correcting for lung transmission) was 9.2 Gy (920 rad).

Case 1

Three months prior to treatment a 51-year-old female developed hoarseness and cough. One month after onset she developed dyspnoea and pyrexia of 37.2°C associated with signs of bronchitis. Her mass-miniature film showed a left pleural effusion confirmed by a full-plate PA chest film (Fig. 1). This was aspirated and found to be malignant and thought to be due to a bronchogenic carcinoma. As other patients treated in this centre had previously been noted to have complete resolution of pleural effusions following upper half-body irradiations for small-cell carcinoma she was accepted for this procedure.

Her forced expiratory volume in one second (FEV_1) was 0.56 litre, 24% of her predicted level. Eight gray (800 rad) were given to the upper half of the body from vertex to umbilicus as described above.

One hour and forty minutes after irradiation she suddenly became dyspnoeic and cyanosed and complained of cold; she then began to shiver. On examination she was cyanosed with Cheyne-Stokes type respiration. Expiratory rhonci were present over the right upper and mid zone; the left pleural effusion was still apparent. No moist sounds were heard. She was able to respond to simple commands. Oxygen and intravenous hydrocortisone 100 mg were administered. After a brief improvement lasting ten to fifteen minutes she gradually became worse and three hours and twenty minutes after irradiation she died.

Autopsy revealed bilateral pleural effusions with dense adhesions. The right lung showed bronchopneumonic changes. The left lung showed a markedly thick pleura over the upper lobe and there was peribronchial thickening extending well into the whole lung. The tracheo-bronchial lymph nodes were enlarged and firm.

Histologically the tumour was undifferentiated causing an extensive fibrous reaction. The only evidence of metastatic spread was to one adrenal gland via lymphatics.

The myocardium was normal apart from a small area of fibrosis. Histological examination of the lungs revealed considerable oedema with proteinaceous fluid in the alveoli and occasional clusters of fibrin material. There was also extensive desquamation of the alveolar lining and many macrophages in the alveoli. There were also changes in the lymphatics due to recent irradiation. Tumour spread throughout the lungs was extensive.

Case 2

A 48-year-old female was referred to the radiotherapy department on the day on which case one was treated. She had had a three-month history of increasing dyspnoea. The plain chest film showed a large left-sided mass and this was confirmed as being due to a small-cell carcinoma of the left upper lobe bronchus (Fig. 2). Physical examination revealed tortuous veins over the left chest wall. There was dullness to percussion over the posterior aspect of the left hemithorax and this was associated with reduced air entry.

Two days after referral she was given 8 Gy (800 rad) to the upper half of the body from the vertex to the umbilicus as described previously. Fifteen minutes later she felt tired and nauseated. She was therefore given Metochlopramide 10 mg intramuscularly. Five minutes later she had a rigor and became cyanosed and dyspnoeic. Physical examination revealed great anxiety, tachypnoea and marked cyanosis. Air entry was good bilaterally and no rales or rhonci were heard. She had tachycardia with normal heart sounds and no added sounds or cardiac murmurs were present. Hydrocortisone 100 mg was immediately administered intravenously. Over the next 15 minutes she became less dyspnoeic but was still cyanosed. Over the following 15 minutes she became more cyanosed and dyspnoeic. Physical examination once again confirmed that both lungs had good air entry and no moist sounds were present. She was empirically given Frusemide 40 mg intravenously on the recurrence of dyspnoea. A pyrexia of 38.6°C was recorded. Ten minutes later her condition had improved and the dyspnoea and cyanosis were less. Thirty minutes later (90 minutes post radiation) she was no longer cyanosed, though still dyspnoeic and pyrexial. Moist sounds were present at the base for the first time since the onset of acute pulmonary distress. At this point cardiac enzymes and an electrocardiogram were arranged. These showed changes consistent with acute pulmonary dysfunction. Gradually she improved through the day although five hours post radiation she was given further intravenous Frusemide (40 mg) and hydrocortisone (100 mg) as her dyspnoea had increased. Her plain film showed the left upper lobe mass and a left basal effusion (Fig. 3).

Twenty-four hours later she again became pyrexial and very dyspnoeic with evidence of bronchospasm and pulmonary oedema. She was given intravenous Frusemide 40 mg and aminophylline 250 mg and started on oral ampicillin and Frusemide. Three days later her pulmonary infection was subsiding. Five days after the upper half-body irradiation she was given 24 Gy (2400 rad) in eight fractions over ten days to the primary and discharged home. One month after discharge she was well with improvement of cough and no abnormal signs on examination. The plain chest film (Fig. 4) showed a great improvement with almost complete radiological remission.

She was also anaemic. Seven weeks post radiation she was admitted, transfused with three units of packed cells and given 8 Gy in a single dose to the lower half of the body from the umbilicus to the soles of the feet. Once again 30 × 30 cm fields on an SL 75 8 MV linear accelerator were used. Three months after the original treatment she was unwell, being very agitated about family problems and had signs of pulmonary infection. The plain chest film revealed left hilar fibrosis only (Fig. 5). She died at home nine days later. A post-mortem was not arranged.

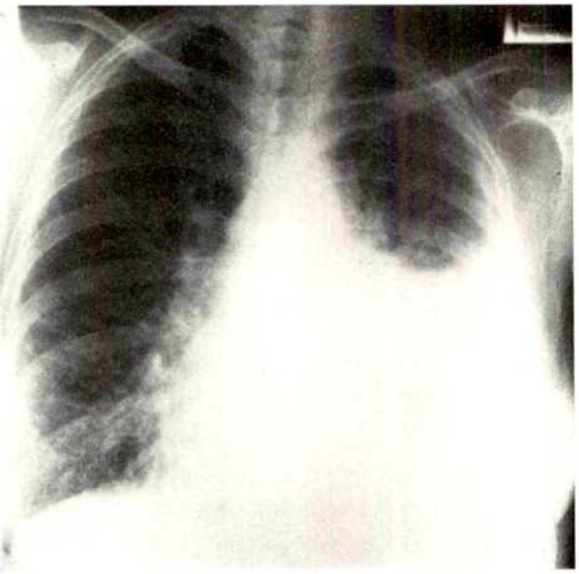

FIG. 1. *Case 1.*
Radiograph film on referral.

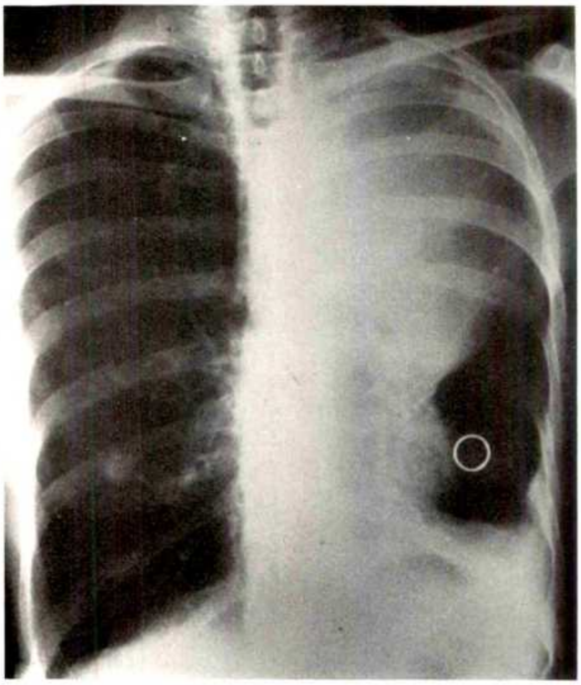

FIG. 2. *Case 2.*
Radiograph film on referral. The metal ring marks the left nipple.

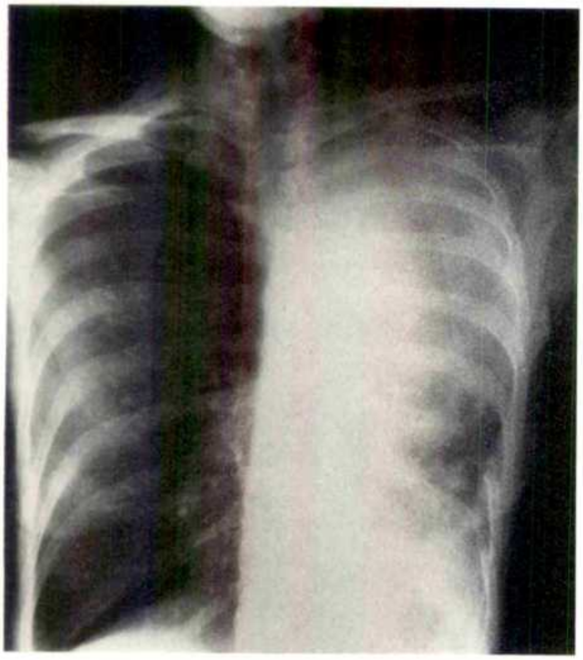

Fig. 3. *Case 2.*

Portable AP chest film taken shortly after a single dose of 8 Gy to the upper half of the body.

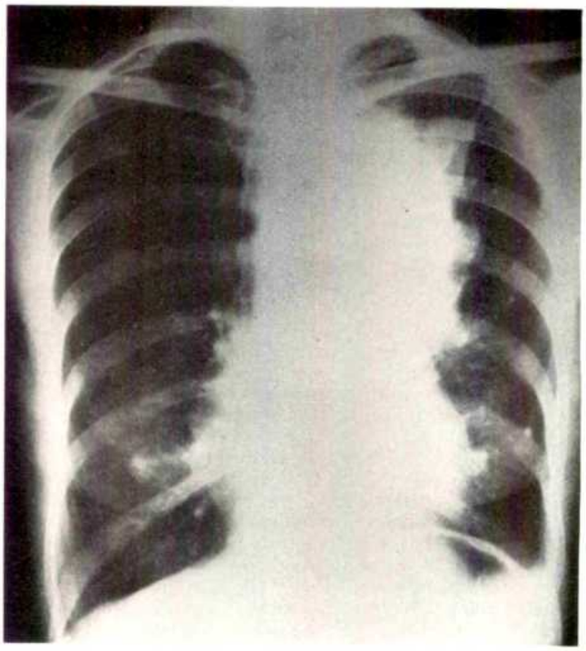

Fig. 4. *Case 2.*

Chest X-ray film one month after upper half body and primary tumour radiotherapy.

Discussion

Warren and Spencer (1940) described a patient with Hodgkin's disease who died the day following a dose of 1.2 Gy (120 rad), given through large fields to the chest using 200 kV X rays. She had been admitted with increasing cyanosis and dyspnoea for two weeks following two previous courses of mediastinal irradiation. Following the dose of 1.2 Gy (120 rad) she became more cyanosed and dyspnoeic and developed pyrexia of 38.3°C and died quickly.

Stone *et al.* (1956) described a patient who received 60 Gy (6000 rad) to the chest in 30 fractions over 43 days using 1 MV X rays. Two days after completion of the course the patient became severely dyspnoeic, started to hyperventilate (40 respirations per minute) and became cyanosed. A pyrexia of 40.5°C was recorded. Basal rales were observed. The plain chest film suggested acute radiation effect. The patient died shortly after the onset of the illness.

Goldman and Enquist (1975) reported a patient undergoing radiotherapy for carcinoma of the right main bronchus with moderate sized fields who, after a dose of 12 Gy (1200 rad) in six daily fractions, developed dyspnoea, a non-productive cough and a fever of 38.3°C. The chest film showed opacification of the right side, most marked in the irradiated area. The patient responded to 40 mg of prednisone and within 24 hours had no symptoms. When the prednisone was stopped he relapsed within 24 hours. This sequence was repeated on two further occasions. They described this as hyperacute radiation pneumonitis.

These cases illustrate the earliest onset of radiation pneumonitis recorded. In retrospect, Warren and Spencer's case was treated with radiation for disease at least in part due to previous radiation. Stone's case probably underwent the latent period, Engelstadt's stage two, during the course of radiation which was six weeks long. Goldman and Enquist's case showed the features typical of acute radiation pneumonitis developing only one week after the onset of radiation and responding to steroid therapy. Only a relatively small part of the lung was irradiated and the latent period was short. The relationship between absorbed radiation dose and normal tissue damage follows a sigmoid curve and the latter two cases probably represent the initial part of this curve.

Following a high single dose of X rays to an organ, the capillaries are damaged leading to the exudation of extra-cellular fluid and diapedesis of red cells. These features were confirmed by Engelstadt (1940) with associated lymph-follicle degeneration and

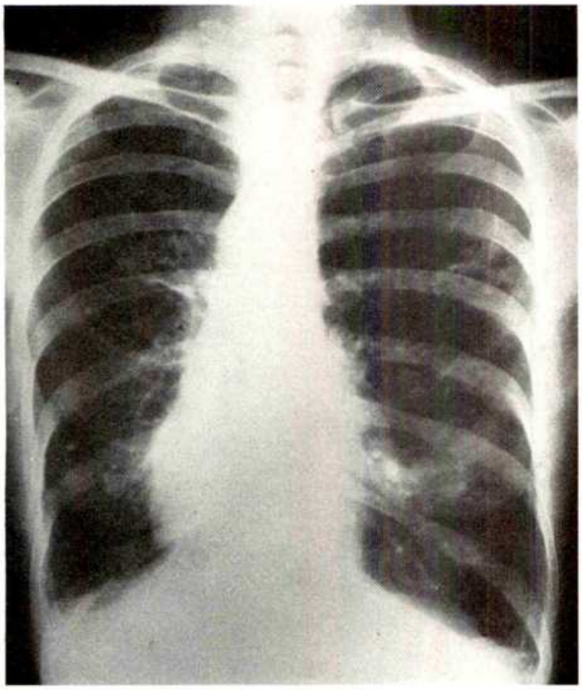

FIG. 5. *Case 2.*

Chest X-ray film three months after irradiation of the upper half-body and the primary tumour.

leucocyte infiltration. In short, a degree of pulmonary oedema occurs. Should the degree of pulmonary oedema be greater or occur in the presence of serious existing pulmonary dysfunction, symptoms will occur. Acute left ventricular failure secondary to myocardial infarction could well produce acute pulmonary oedema, but in the first case the myocardium was normal and in the second case the electrocardiogram and cardiac enzyme studies confirmed an acute pulmonary event. Both cases had extensive pulmonary disease and the response of the second case to Frusemide suggests that exudation following radiation was sufficient to distress both patients severely and cause the death of one.

SUMMARY

Two patients who received single uncorrected doses of 8 Gy to the mid-plane of the lungs developed acute pulmonary distress characterized by the sudden onset of dyspnoea and cyanosis associated with pyrexia and also with rigors. Auscultatory evidence of pulmonary oedema was not present initially. These events occurred within two hours of irradiation. One case proved fatal. Myocardial damage did not feature in either case. Supportive therapy with steroids and a quick-acting diuretic were life saving in one case. These effects are probably due to alveolar capillary damage leading to pulmonary oedema in the presence of existing severe pulmonary dysfunction.

ACKNOWLEDGMENTS

I would like to thank Dr. R. G. B. Evans of the Radiotherapy Department for permission to report one of the cases who was under his care when seen, Dr. M. Lesna for reviewing the post-mortem findings, and Mrs. H. Harrison for typing the manuscript.

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Book review

Why be quantitative about radiation risk estimates? By Sir Edward E. Pochin. The Lauriston S. Taylor Series in Radiation Protection and Measurements. Lecture No. 2, presented March 15, 1978, issued July 1, 1978, pp. 36 (NCRP Publications, Washington), $6.00.
ISBN 0-9133-9242-1

This is a short and easily readable account of the bases underlying the current recommendations of ICRP. Information buried in ICRP 26 and 27 is brought out in a simple way. There are individual sections on the risk per rad of developing leukaemia and cancer of the thyroid, breast, lung, bone and other organs, with a short explanation of the data on which the estimates are based. A final section compares risks from radiation with the risks of working in different types of industry and with the risks attached to voluntary activities such as smoking and travelling by car.

D. K. BEWLEY.

1979, *British Journal of Radiology*, *52*, 880–887

Contrast enhancement of high-energy radiotherapy films

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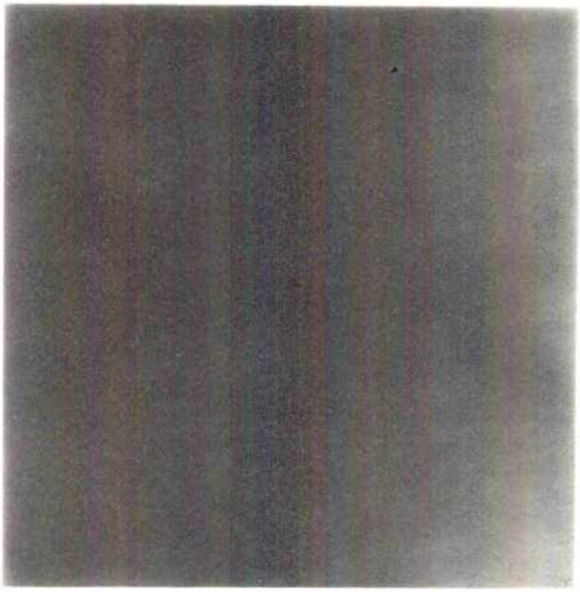
ABSTRACT

An order-of-magnitude improvement in the contrast of high-energy localization and verification films has been achieved through the application of a simple, inexpensive, contrast enhancement technique. The method involves making reversal contact "prints" of the original film onto ordinary X-ray film with equipment commonly available in any radiotherapy department. This results in "gamma multiplication". The theory as well as several applications of this effect are presented.

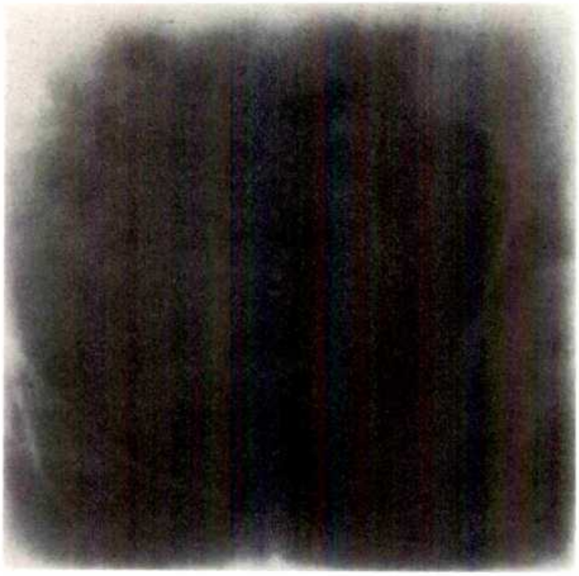
Verification films taken during treatment are essential for the precise localization of radiotherapy treatment fields. Yet, with very high-energy X-ray beams, the differential attenuation between the various body tissues is not sufficient to produce images with enough useful anatomical detail to enable one to be confident of accurate field localization. This is especially true at energies greater than 4 MeV, and particularly through the thicker parts of the body. This is demonstrated by the typical 10 MeV pelvic verification film shown in Fig. 1A.

Due to the importance of these films, many attempts have been made to improve their quality. For example, contrast of the anatomical region being visualized can be improved by introducing into (or onto) the patient, high-density materials such as metal sounds in the uterus, mercury in the bladder, lead markers on the skin, etc. Although these are frequently helpful, much valuable internal anatomical detail is still absent. Furthermore, these contrast media cannot be used for verification films exposed during treatment, since they would alter the dose distribution within the patients.

An alternative approach is to increase the contrast of the imaging system to such a degree that small changes in the attenuation of anatomical features are rendered visible. With film as the imaging device, small increases in film contrast have been obtained through careful choice of metal screens (Hammoudah and Henschke, 1977; Droege and Bjarngard, 1977; 1978) or light-emitting screens (Galkin *et al.*, 1978). The effective contrast of these films can be doubled using a method reported by Strubler *et al.* (1977). In this technique a duplicate of the original is made with radiographic copy film. The original and the copy are sandwiched together (they must be precisely aligned) and imaged using a bright light viewing system. All of these methods have been only marginally useful.



(A) 10 MeV verification film of a pelvic field.



(B) The same film after contrast enhancement.

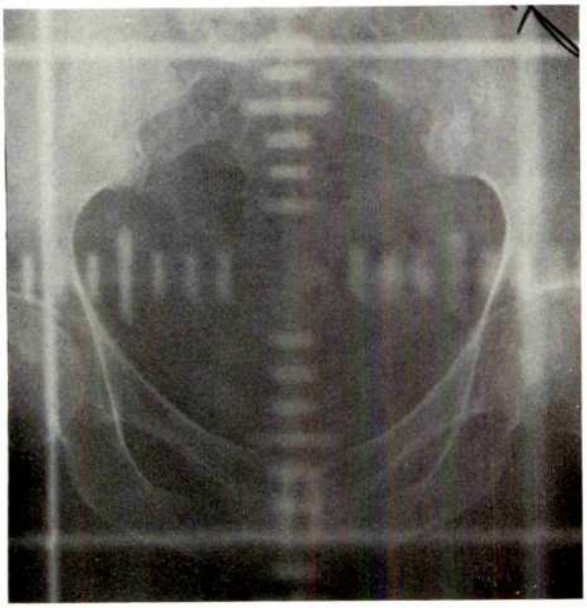


FIG. 1

(c) Simulator film showing the planned field.

There have also been some studies into the use of electronic contrast enhancement, either by the use of electro-optical discrimination techniques (Maddox, 1978) or computer manipulation of images (Greer and McShan, 1978). These methods are both expensive and time consuming, and have not been shown to be useful outside the experimental laboratory.

This paper introduces a simple, rapid, and inexpensive method for greatly enhancing the contrast of ordinary localization and verification films. The technique produces films with an order-of-magnitude increase in contrast, sufficient to visualize anatomical detail at any X-ray energy used in radiotherapy. This is illustrated by Fig. 1B, which was obtained directly from the film shown in Fig. 1A using only the facilities already found in most radiotherapy departments. It is interesting to note that in this example the field treated (Fig. 1B) does not correspond to that planned at simulation (Fig. 1C). This "geometrical miss" could well have escaped detection if the original verification film alone (Fig. 1A) had been available for review.

The method also has the advantage that any desired optical density for the final radiograph can be selected, regardless of that of the original film. Over- or under-exposed films are usually salvageable, and the need for repeat exposures is minimized.

METHOD

The basic principle

The method is based upon the principle of "gamma multiplication", which results from successive contact "printing" of radiographs onto unexposed film. The theory of this phenomenon is given in the appendix, and it is illustrated diagrammatically in Fig. 2. The "gamma" is a convenient parameter used to represent the inherent contrast of film. It is defined as the slope of the characteristic (or H & D) curve of the film in the region of interest. Typical characteristic curves for the films used in this paper are shown in Fig. 3. For example, in film 1 (Fig. 2A), if D_1 and D_2 represent the optical densities of points of interest which received slightly different exposures, then the gamma is the slope of the curve between D_1 and D_2. For this example, therapy verification film is used (Kodak XV) which has a gamma (γ_1) of 2.3 in the optical density region of interest (about 1.5).

The first enhancement radiograph (film 2) is obtained by making a contact "print" of film 1 on an unexposed film (in this example therapy localization film Kodak XTL*). This is achieved by placing film 1 over the unexposed film 2 and exposing the combination to a pre-determined quantity of visible light (specific techniques are described later). Figure 2B shows the densities of the points of interest on film 2 plotted against log (initial X-ray exposure). The slope of this curve (effective contrast) is the product of the gammas of the two films ($\gamma_1 \gamma_2$), in this case 2.3×3.5 (as can be determined from the characteristic curves in Fig. 3; XTL, at a density of 1.5, has a gamma of 3.5). Note also that the slope is negative, indicating that the film is a reversal of the original.

The final enhancement radiograph is obtained by repeating the process, *i.e.*, making a contact print of film 2 onto unexposed film (Kodak XTL in this example). Since $\gamma_3 = 3.5$, the resultant effective contrast, given by $\gamma_1 \gamma_2 \gamma_3$, is 28. Contrast has been increased by a factor of about 12. The two stages of the enhancement process are illustrated by the radiographs in Fig. 4.

Apparatus and techniques

Almost no additional equipment is required other than that found in most radiotherapy (or radiology) departments, *viz.* the white lights in a darkroom, a timer (watch, stop-watch, etc.), and a densitometer.

The physical set-up is illustrated in Fig. 5. The film to be enhanced is placed over the appropriately selected unexposed film on a table beneath the lights.

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*This emulsion is identical to that of Kodak M (mammographic) film.

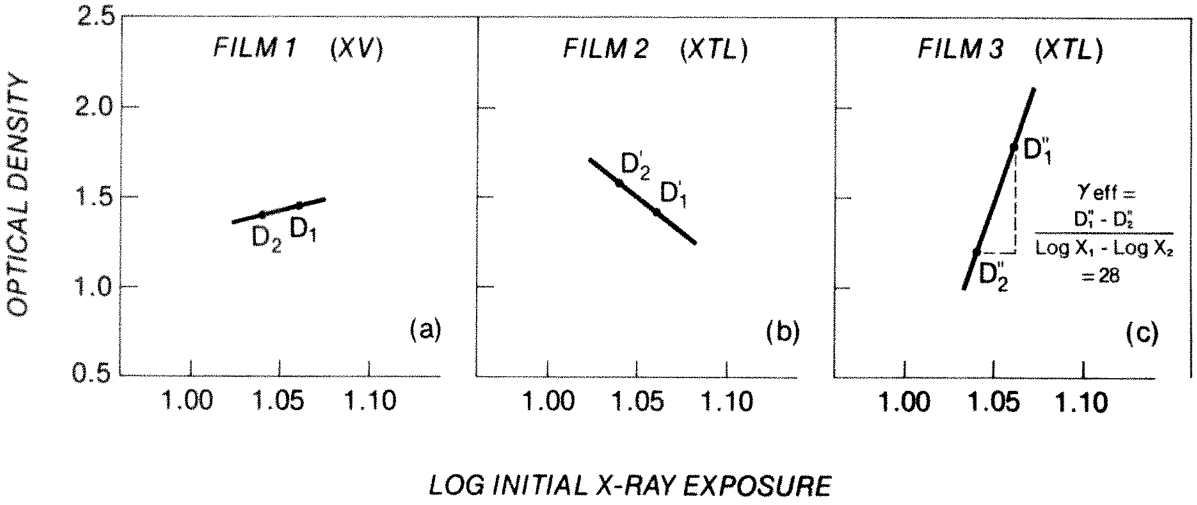


Fig. 2.

Diagrammatic representation of the "effective" characteristic curves (plotted against the log of the initial X-ray exposure) for each stage of a typical contrast enhancement process.

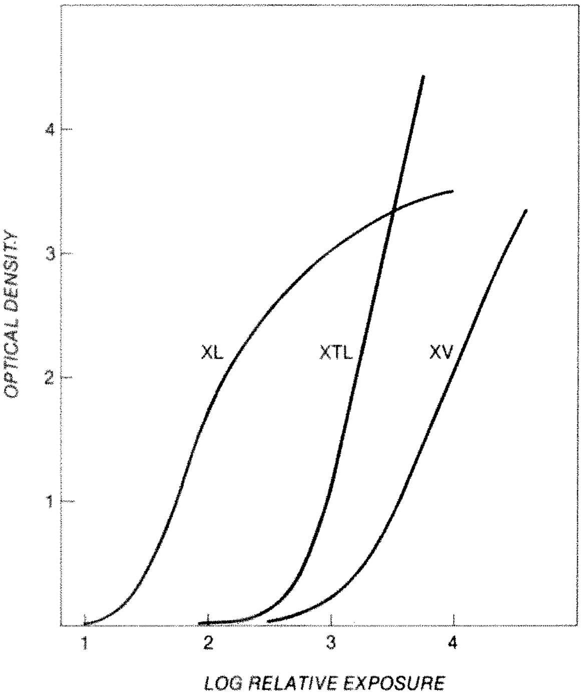


Fig. 3.

Measured characteristic curves (background subtracted) for three Kodak radiographic films exposed to visible light.

The lights are then switched on for a predetermined period of time, which depends on the density of the area of interest on the original radiograph (measured with the densitometer) and on the desired density of the enhancement film.

Several improvements in this basic set-up have been added to make the procedure more reproducible and the images sharper. For example, good contact between the two films is essential, and this can be achieved by placing the films in a suitable filmholder (a plywood frame) and sandwiching them between a $\frac{1}{4}$ in thick sheet of black rubber (*e.g.* Neoprene) and a heavy sheet of plate glass, as shown in Fig. 5. The black rubber also prevents fogging caused by light reflected off the bottom surface of the film holder. Some forms of commercially available contact print frames are ideal for this purpose.

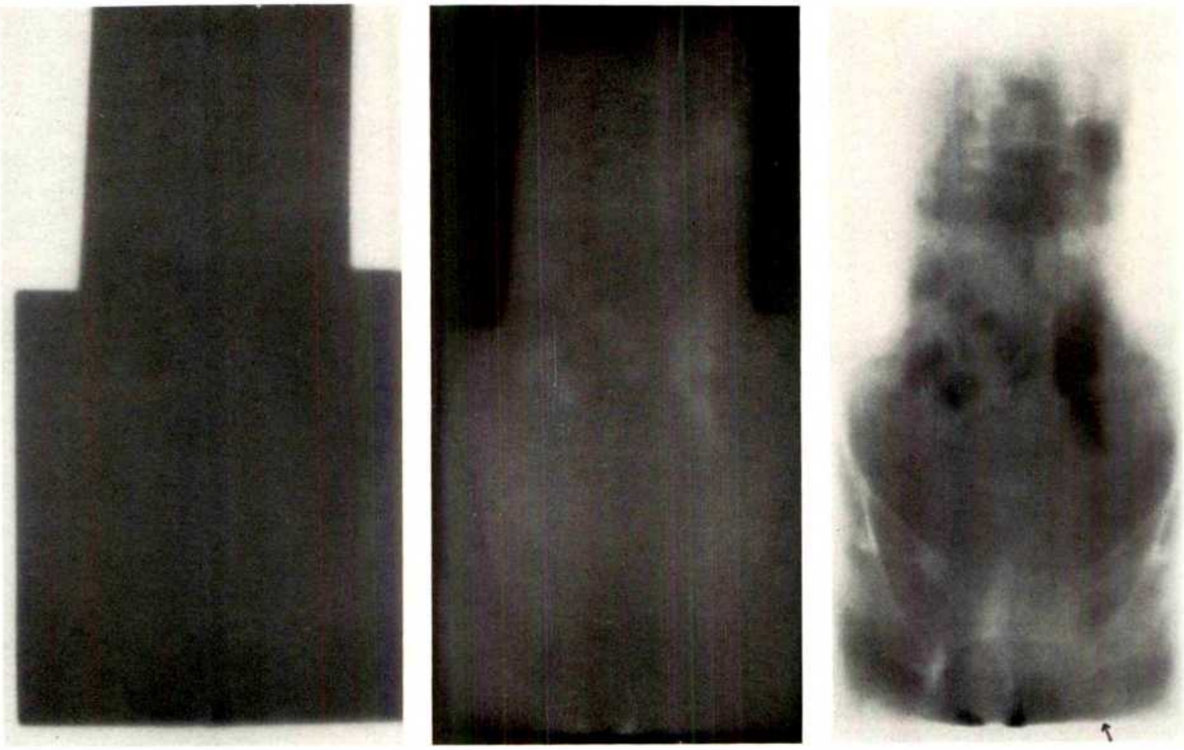
In order to obtain exposure times which are long enough to be accurately reproduced (especially when fluorescent lights are used), it is sometimes necessary to reduce the intensity of the incident light by covering the glass with a neutral density filter. A uniformly exposed radiographic film will serve this purpose. It is convenient to generate a table of these exposure times for each type of film which is used. A typical set of times for XTL film is shown in Table I. Users will have to generate their own tables and may find that a photographic step wedge (or tablet) greatly facilitates this process. It should be noted that only one entry on each table need be determined by experiment. The other values can be derived from it using the definition of optical density (OD):

$$\text{OD} = \log_{10} \frac{\text{incident intensity}}{\text{transmitted intensity}}$$

There are many refinements which can be added to this system to make it more versatile. For example:

(a) an adjustable intensity light source with an exposure meter to eliminate the need for long exposure times. This may be used with constant exposure times by measuring, and appropriately adjusting, light transmitted through the radiograph being enhanced;

(b) an electronic timer wired into the light switching system;



A B C

FIG. 4.

(A) Pelvic and para-aortic 10 MV verification film.
(B) The first enhancement (reversal) of this film.
(C) The final enhancement of this film (the arrow points to one edge of a plastic colostomy tube lying on the abdomen of the patient).

TABLE I

A SAMPLE TABLE OF TIMES OF EXPOSURE TO LIGHT (IN SECONDS) FOR PRODUCING A DENSITY OF 1.5 ON KODAK XTL FILM.

Density of filter selected	Density of interest on original												
	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0
0.0 (no filter)	—	—	—	—	—	—	—	7	11	18	28	44	70
1.0	—	—	7	11	18	28	44	70	111	—	—	—	—
2.0	28	44	70	111	—	—	—	—	—	—	—	—	—

Neutral density filters are used to keep exposure times in a convenient range. The values are dependent on the intensity of the light source and thus each facility will need to have similar tables constructed as outlined in the text.

(c) a self-contained light exposure system, such as a subtraction/duplication box, or a contact printer.

It should be noted, however, that if a dimmer switch is used to adjust the intensity of tungsten lamps, the colour of the light changes with the intensity. Since film and light meters have different spectral responses, this technique leads to complications.

Tests are currently being performed using several other methods to control light exposures automatically. This automatic contrast-enhancement system will be reported in a future publication.

Film selection

Although the method will work with almost any type of X-ray film, the best results are obtained with specific combinations of films. For the initial radiograph, since the film is usually chosen more for its speed than its contrast, the type of emulsion is not specifically selected for contrast enhancement. For verification films, Kodak XV (or equivalent) is used, whereas for localization films a medium speed film, such as XTL, is appropriate.

On the other hand, the type of film used for the first enhancement (film 2) requires careful selection. The choice depends on how much contrast is required in the final enhancement, and conversely, how much latitude can be sacrificed in order to obtain this contrast. For example, if the original radiograph has so little contrast that the absolute maximum enhancement is required, the film with maximum gamma should be used. As shown by the characteristic curves illustrated in Fig. 3, this would be Kodak XTL (or its equivalent) at high density. Furthermore, XTL film should be used again in the last step of the enhancement procedure to continue maximizing the contrast. However, for most films taken during treatment, the contrast which results from this choice will be excessive and the latitude too narrow. The use of a wide latitude film (such as Kodak XL) for the final step diminishes this problem considerably. The characteristic curve for this type of emulsion has a steep slope (high gamma) for most densities below 2.0 (Fig. 3) and a lower gamma for high densities. By using XTL for the initial enhancement and XL for the final step, a compromise between high contrast and wide latitude is obtained. This has been found to be useful for most radiotherapy film applications.

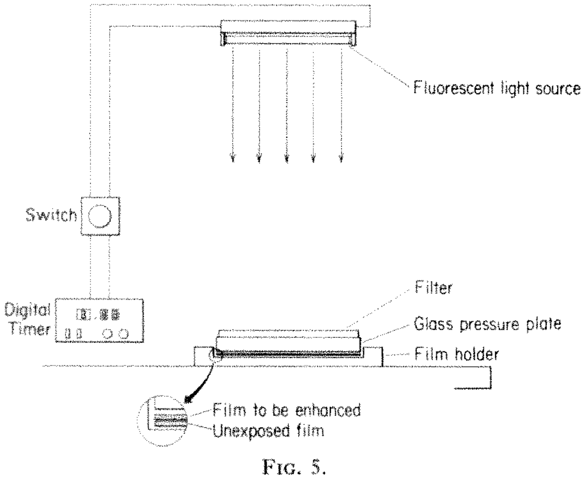


Fig. 5.

Schematic drawing of a typical contrast enhancement set-up in a darkroom. The film holder is plywood with Neoprene rubber. The digital timer is optional. Tungsten lamps can be substituted for the fluorescent lights if desired.

Results

Example

Figures 4A, B, and C illustrate a typical example of the enhancement process. The original film (A) shows virtually no anatomical detail. The first enhancement (B) probably reveals enough bony structure for a determination of the adequacy (or inadequacy) of the coverage of the field with respect to the pelvic sidewalls. The final film (C) contains sufficient contrast to make out the pelvic sidewalls, the vertebral interspaces, and even the image of a plastic colostomy tube on the abdomen of this patient.

Careful examination of Fig. 4 will show that there is an apparent shrinkage of the radiation field with each enhancement. This is a direct result of the increased contrast, and hence decreased latitude, of each successive enhancement. Only that part of the field which is uniformly exposed (approximately within the 90% isodose) is visualized on the final enhancement. However, since such verification films are supposed to indicate the extent of the planned tumoricidal dose region, this is not a disadvantage but rather a desirable feature of the contrast enhancement system. If for any reason it is desired to visualize the edge of the radiation field as it appears on the original film, a dark line can be drawn around the perimeter of the field before commencing enhancement. This line will then appear on the final film. Alternatively, use of XL for film 2 and film 3 will usually give enough latitude to render the beam edges visible.

Verification of the gamma multiplication effect

An experiment was designed to test the accuracy of "gamma multiplication" in predicting the effective gamma. A verification film of a thin aluminium step wedge was made with 10 MV X rays on XV film. The exposures under each step of the wedge were measured with a small ionization chamber. The step wedge was made thin enough that the entire range of exposures to the film through the wedge was less than 5%.

Using the methods already described, the verification film (film 1) was enhanced (on XTL) to yield film 2, and this was enhanced (on XL) to produce film 3. The optical density of the image of each step was measured by densitometer for each of the three films.

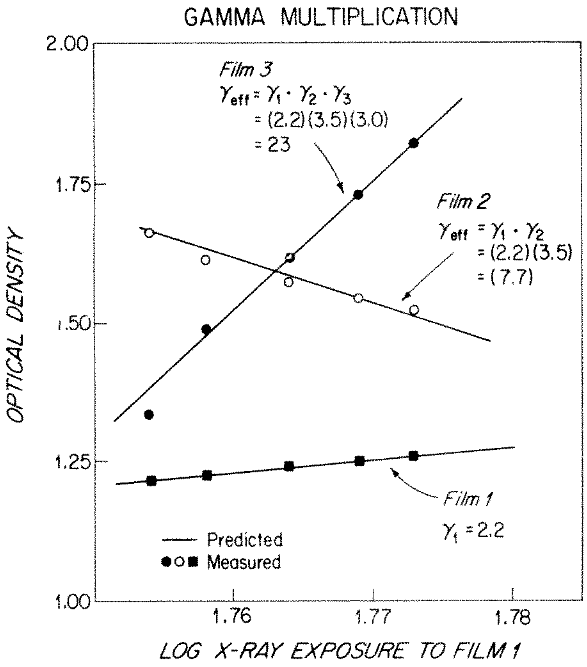


FIG. 6.
Step-wedge experiment demonstrating "gamma multiplication".

The data points plotted in Fig. 6 are measured optical density values on the original and enhanced films, and these are shown plotted against the log of the initial X-ray exposure. The solid lines for films 2 and 3 are the "effective" characteristic curves theoretically predicted by "gamma multiplication". Their slopes are $\gamma_1 \gamma_2$ and $\gamma_1 \gamma_2 \gamma_3$ respectively, and these are the "effective contrasts" of the radiographs. The agreement between the experimental points and the theoretical lines demonstrates the "gamma multiplication" concept.

DISCUSSION

In an age when radiological physicists are concerned with errors in dosimetry of ±1% or less, it is superfluous to point out the importance of ensuring that radiotherapy treatment beams actually "hit" all of the planned target all of the time. Yet films used to check beam positioning frequently lack enough contrast to make reliable judgments possible. A simple method of enhancing the contrast of high-energy radiotherapy films has been developed. This increase in contrast is not achieved without sacrifice, however. For example, high contrast is synonymous with low latitude. Furthermore, not only is the useful information on the film enhanced, so also is the noise. Processor induced imperfections, scratches, etc., which are not normally noticed, are obvious in the contrast enhanced film. Finally, there is an inherent loss in resolution whenever films are copied, although this is not a problem with radiotherapy images which are contrast, and not resolution, limited.

Several other applications of this contrast enhancement technique are under investigation, including:

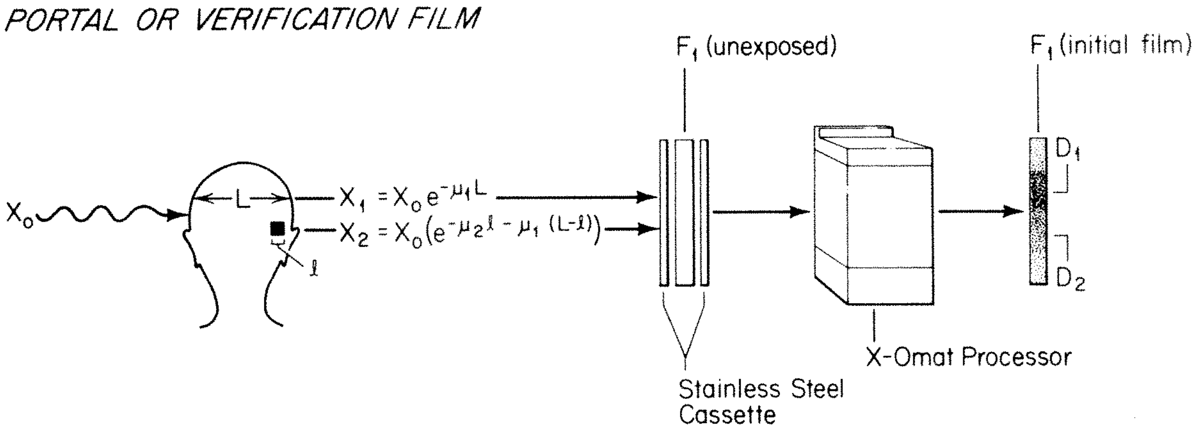


FIG. 7.
Schematic representation of the production of a typical radiotherapy film.

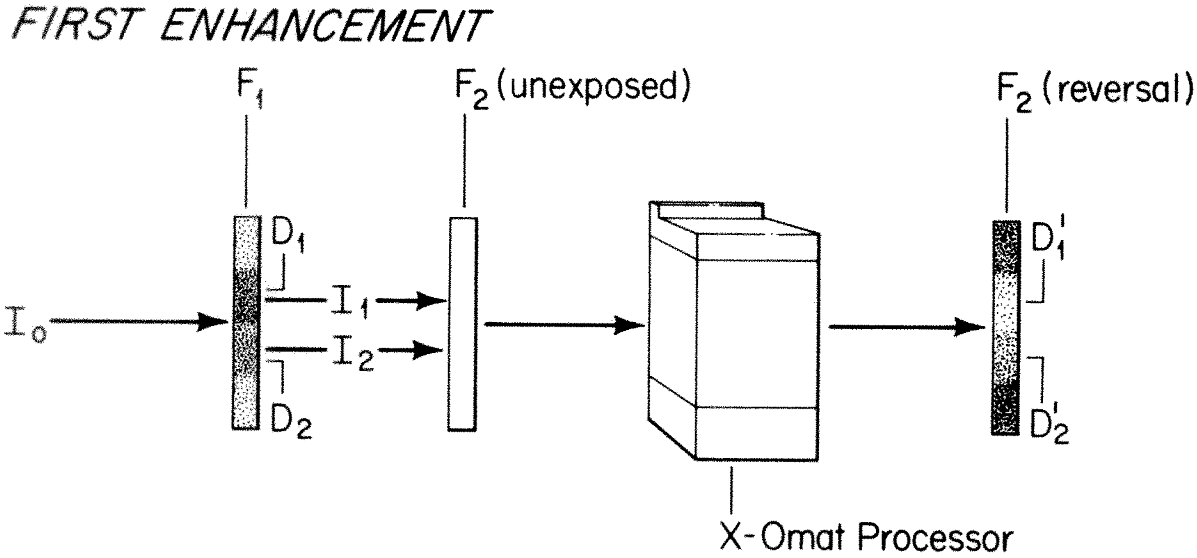


Fig. 8.
Schematic representation of the production of the first enhancement film.

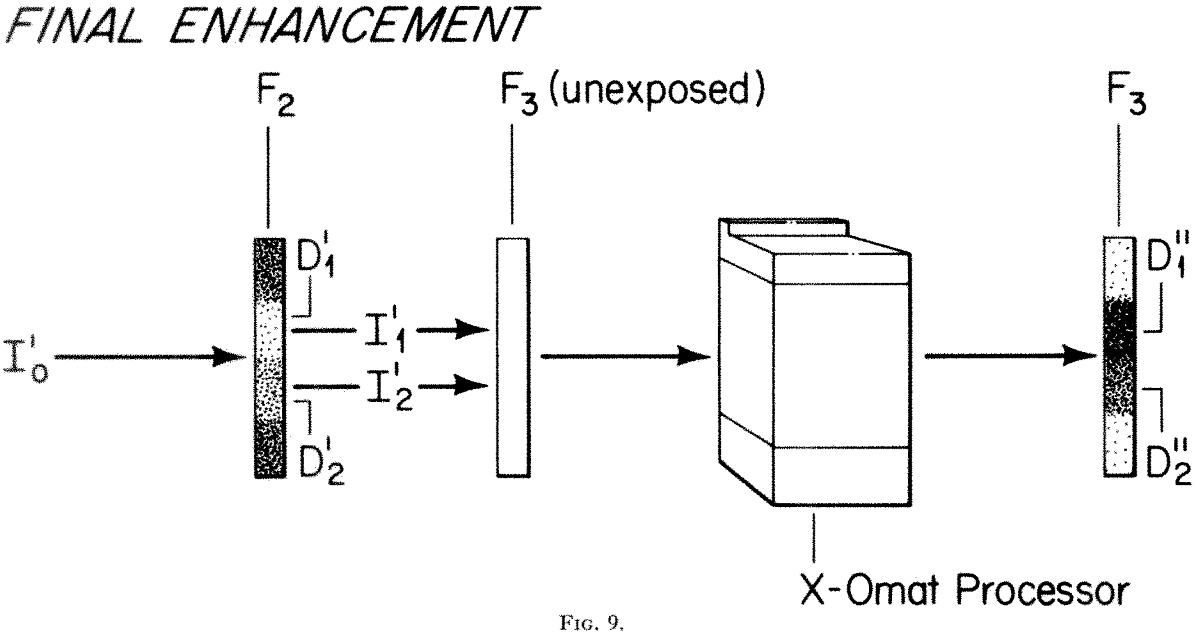


Fig. 9.
Schematic representation of the production of the final enhancement film.

(a) enhancement of the contrast of diagnostic radiographs. This is especially useful in mammography for increasing the visibility of "suspicious" areas of mammograms;

(b) salvage of incorrectly exposed radiographs (verification, localization, simulator, and diagnostic films). Radiographs which have sufficient contrast but are too light or too dark can be reproduced at any desired density by employing only the first step of the contrast enhancement procedure using radiographic "copy" film. For films also lacking contrast, the normal contrast-enhancement technique can be used.

APPENDIX

The contrast enhancement technique is illustrated diagrammatically in Figs. 7–9. Figure 7 shows the production of the initial film (the stainless steel cassette serves only to produce a sharp image). Consider for simplicity that two adjacent areas on film F_1 receive slightly different X-ray exposures X_1 and X_2. After the film is developed, these two areas have optical densities, D_1 and D_2, respectively.

The values of X and D are empirically related through the gamma of the characteristic (H & D) curve, where the γ represents film contrast. For film F_1, γ_1 is the slope of the characteristic curve between the densities D_1 and D_2, *i.e.*

$$\gamma_1=\frac{D_1-D_2}{\log X_1-\log X_2} \quad . \quad . \quad . \quad . \quad (1)$$

In the enhancement process, a "contact print" of the original (F_1) is made by passing light of intensity I_0 through F_1 on to an unexposed film F_2. This is illustrated schematically in Fig. 8. In this simple case, the light intensities passing through the two areas of optical density D_1 and D_2 are I_1 and I_2, where, from the definition of optical density,

$$D_1=\log(I_0/I_1) \text{ and } D_2=\log(I_0/I_2) \quad . \quad . \quad . \quad (2)$$

After film F_2 is developed, the resulting optical densities of the two areas under consideration are D_1' and D_2'. F_2 is a "reversal" of F_1, *i.e.*, if $D_1>D_2$, then $D_2'>D_1'$. The characteristic curve for film F_2 relates the densities D_1' and D_2' to the visible light exposures these regions received, E_1 and E_2, respectively. Assuming that these exposures are in a region of the characteristic curve which can be approximated by a straight line, the values of D and E are related by:

$$\gamma_2=\frac{D_1'-D_2'}{\log E_1-\log E_2} \quad . \quad . \quad . \quad . \quad (3a)$$

Since E represents an exposure of the film to intensity I_0 for a period of time, Δt, $E_1=\Delta t \cdot I_1$ and $E_2=\Delta t \cdot I_2$.

$$\therefore \gamma_2=\frac{D_1'-D_2'}{\log I_1-\log I_2} \quad . \quad . \quad . \quad . \quad (3b)$$

In the final stage of the contrast enhancement process, a "contact print" is made of the reversal film, F_2, onto an unexposed film, F_3, as illustrated in Fig. 9. The intensities of the light passing through regions of density D_1' and D_2' on F_2 are I_1' and I_2', respectively, and when the final film, F_3, is developed, the optical densities of the corresponding regions are D_1'' and D_2''. On this final film, the density "polarity" of the original film is retained, that is $D_1''>D_2''$. By using the same reasoning as with the first stage of enhancement, the quantities D'' and I' are related through the γ of the characteristic curve for film F_3:

$$\gamma_3=\frac{D_1''-D_2''}{\log I_1'-\log I_2'} \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The "effective contrast" represents the optical density difference on the final film which results from the small difference in X-ray exposure of the initial film, *i.e.*:

$$\gamma_{\text{eff}}=\frac{D_1''-D_2''}{\log X_1-\log X_2} \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Then from eqns. 1, 2, 3b, 4 and 5 and the definition of OD,

$$\gamma_{\text{eff}}=\gamma_1\ \gamma_2\ \gamma_3$$

The resultant "effective contrast" is, therefore, obtained by "gamma multiplication."

ACKNOWLEDGMENTS

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Radiation dose to critical organs of staff and patients during neuroradiology

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ABSTRACT

The doses delivered to some critical organs of patients and staff during cerebral angiography, X-ray computer assisted tomographic scanning and ^{99}Tc^{m} brain scanning have been measured or assessed.

The results show that doses received by staff and by the patients' gonads are generally quite low. However, patients having two or more of the investigations could receive skin and orbit doses in excess of 25 rad.

In 1960, when the Adrian Committee was considering the doses involved in the various clinical uses of X rays, the only type of neuroradiological examination warranting measurement was that of angiography. It was reported that the gonad dose to the population from this examination was negligible and the skin dose per examination was on average one rad. Since these figures were obtained, not only have the techniques of neuroradiology altered, but other forms of investigating the central nervous system by X-ray tomographic scanners and isotope scanners have become generally available. Attention has already been drawn to eye doses received in neuroangiography (Isherwood *et al.*, 1975; Bergstrom *et al.*, 1972) and this paper describes an attempt to look at the total doses that could be received during cerebral investigations at Aberdeen Royal Infirmary.

CEREBRAL ANGIOGRAPHY

Technical advances now allow techniques to be used in cerebral angiography that were impossible at the time of the Adrian report. Television fluoroscopic intensifiers allow catheters to be inserted and screened via the femoral artery, and higher output generators, together with serial film changers, have increased the number of radiographs and the speed at which they can be taken. This has led, not only to the patient receiving higher doses, but also to potentially increased exposure for the radiologist performing the investigation.

At Aberdeen Royal Infirmary cerebral angiographic procedures are carried out under a general anaesthetic. If femoral catheterization is not being performed the radiologist usually stands on the patient's left side with the assisting nurse on the opposite side, both approximately adjacent to the patient's shoulders. Both stand behind protective "pulpit" screens, and in addition a lead-rubber panel, run on a pulley system, is lowered between the patient's head and the radiologist. This panel is shaped so as to fit round the patient's neck and under ideal conditions touches the table. However, it may be obstructed at chest level by anaesthetic tubes, depending on the size and shape of the patient, in which case the neck aperture may allow radiation through. Under average conditions the exposure in the region of the patient's chest for a basic series of 16 radiographs is too low to be recorded accurately. However, with the panel in its worst position the dose is quite high as shown in Fig. 1. The usefulness of this panel became apparent when, due to technical reasons, the work had to be carried out for a week in an alternative theatre where such a panel was not installed.

Eight radiographs are usually taken for each of the AP and lateral projection series, the AP series usually being taken first. A single lateral view of the neck is often taken to show the bifurcation of the common carotid artery, in which case a further injection of contrast medium is given.

If multivessel angiograms are required, further sequences of films will be taken while contrast medium is injected into the other carotid and vertebral arteries. Oblique views with the beam centred on the orbit of the side being investigated are also sometimes required. For vertebral artery injections the AP view is replaced by the Towne's view.

Thus, depending on the nature and purpose of the investigation, the number of radiographs taken can range from 16 to 60 with, in some cases, the addition of fluoroscopy.

The proximity of the radiologist to the patient during the exposures means that he will be exposed to scattered radiation. When the femoral artery is used for injection of contrast medium the exposure is small relative to that when the carotid artery is used. During the injections of contrast medium into the

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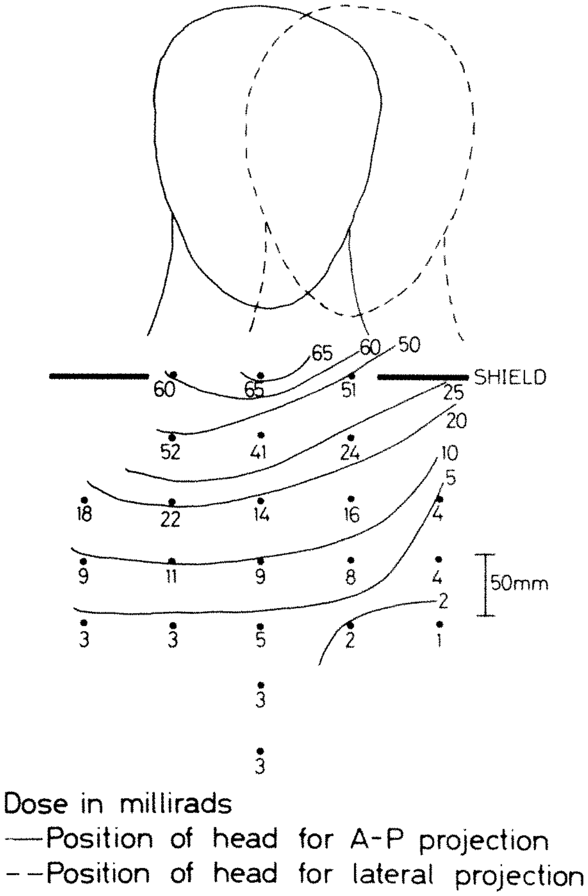
65
60
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SHIELD
60
65
51
25
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52
41
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5
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22
14
16
4
9
11
9
8
4
2
50mm
3
3
5
2
1
3
3
Dose in millirads
—Position of head for A-P projection
--Position of head for lateral projection

FIG. 1.

Distribution of dose at the surface of the patient's chest with the shield in the "worst case" position for a standard examination with 16 radiographs. For the lateral view, the position of the head relative to the shield is changed because the patient is moved nearer to the serial film changer. When the shield is in the optimum protective position, pulled down over the patient's neck, the shield would move with the patient and this relative shift would not occur; in the optimum situation the scattered radiation dose is too low to be recorded accurately.

carotid artery the radiologist's hands are often close to the patient's head and neck, so that despite the use of the lead-rubber screen and careful collimation a significant dose to the fingers can be received. This is particularly the case when the radiologist manually compresses the opposite carotid artery in order to see the cross-circulation, for at these times his hand may be beyond the lead-rubber panel. All other personnel retire behind lead screens when radiographs are being taken. When fluoroscopy is being used all personnel wear lead-rubber aprons.

Dose measurements

Film badges worn by the theatre staff to measure whole-body dose rarely record any radiation and further investigation of these doses was not made. Using TLD chip dosimeters the doses to the finger and eye of the radiologist, and to the eye and gonads of the patient, were measured. The eye dose of the radiologist was measured in accordance with the recommendations of Dunlap (1975) by attaching the dosimeter to the collar.

The TLD dosimeters used were Harshaw 100 chips. The lowest dose recordable was 5 mrad and doses were read with an accuracy of at least 5%. The gonad dose was measured approximately by placing a dosimeter above the ovaries in the case of female patients and fastening one near to the testes in the case of male patients.

The results of the first series of measurements on patients are summarized in Table I. Even when fluoroscopy was used during bilateral investigations with catheterization through the femoral artery the gonad dose to the patient was very small. The situation regarding this is still the same as that reported by the Adrian Committee survey, *i.e.* the contribution to population gonad dose from neuroradiological procedures is negligible. The number of films taken now, however, is very much larger. For all the measurements summarized in Tables I and II, the minimum taken was 16, the maximum 64, with a median of 21 for left carotid angiography, 18 for right carotid angiography, 40 for bilateral carotid angiography and 56 for bilateral carotid and vertebral angiography.

The eye doses summarized in Table I are similar to those reported elsewhere (Isherwood *et al.*, 1975; Smith *et al.*, 1976) and it was decided to investigate the use of eye shields where possible. These were pre-formed from 2 mm lead sheet which was bent and cut to the approximate shape of the eye and coated with a layer of plastic. The eye doses received following the introduction of these shields are summarized in Table II. As can be seen the shield generally reduced the doses by 50%, and in some cases by 90%, depending upon the type of investigation. The shields were placed over the eye opposite to the side of the head being investigated, and so served to reduce the dose to that eye by 80–90% in unilateral carotid angiography. In bilateral angiography the dose was reduced by up to 45% as the lead shield had to be transferred from one eye to the other when the opposite artery was injected. In order to determine the reduction of dose in each particular type of examination one dosimeter was placed on the eye and a second on top of the eye shield. Both Tables I and II show that the right eye always received more than the left as it was closer to the X-ray set when lateral films were taken.

The dose received by the radiologist's finger per examination was found to be quite small, but with two or three lists per week each with three or four patients the dose could rise as high as 150 mrad per week, i.e. 7.5 rad per year. The efficiency of the lead-rubber panel in reducing this dose was seen when the operations were carried out in a theatre without this facility. The doses recorded were generally higher and a much higher total finger dose was experienced for the week. The average increase per radiograph was from 0.5 to 0.8 mrad and 0.6 to 1 mrad for right carotid and bilateral carotid injections respectively. An increase in the dose at the radiologist's collar was also recorded when this theatre was used. Doses at the collar were recorded in all the investigations in this theatre, one as high as 20 mrem. Normally the collar dose was either just detectable or not detectable at all.

X-RAY COMPUTER ASSISTED TOMOGRAPHIC SCANNER

The Mark I EMI Scanner, installed at Aberdeen Royal Infirmary during the period these measurements were taken, used a water-filled head support and was operated at 120 kV, 35 mA. The initial

TABLE I

SUMMARY OF DOSES RECEIVED BY PATIENTS DURING CEREBRAL ANGIOGRAPHY BEFORE USING EYE SHIELDS

		Left carotid angiography	Right carotid angiography	Bilateral carotid angiography	Bilateral carotid vertebral angiography
Right eye (rad)	median range	8.80 5.90–13.70	7.60 4.50–9.90	12.70 12.35–19.20	22.50 18.10–25.80
Left eye (rad)	median range	6.30 4.20–8.30	4.10 3.80–6.70	7.70 7.50–8.60	13.00 9.00–18.50
Number of observations		4	5	3	6
Number of radiographs	median range	21 17–25	18 16–24	33 32–40	50 40–64
Screening time (min)	median range	— —	— —	— —	7.75 2.50–12.00

TABLE II

SUMMARY OF THE REDUCTION BY LEAD EYE SHIELDS OF DOSES TO PATIENTS' EYES DURING CEREBRAL ANGIOGRAPHY

		Doses (rad) under and above lead shields							
		Left carotid angiography		Right carotid angiography		Bilateral carotid angiography		Bilateral carotid vertebral angiography	
		under	above	under	above	under	above	under	above
Right eye (rad)	Median	0.62	5.0	—	8.5	8.6	15.8	13.9	20.3
	Range	0.55–0.74	4.1–7.7	—	6.7–12.6	6.0–17.3	8.1–27.0	—	—
	Average reduction	88%		—		45%		31%	
Left eye (rad)	Median	—	4.9	1.2	5.6	5.25	12.5	9.9	15.5
	Range	—	4.2–5.8	0.6–1.32	2.35–7.9	4.6–10.4	7.9–19.8	—	—
	Average reduction	—		78%		58%		36%	
Number of observations		3		4		7		1	
Median number of radiographs per examination		17		22		40		56	

scans were sometimes repeated using contrast medium, with a further scan being made on rare occasions. The room was purpose designed so that there is very little exposure to the radiologist or radiographer. Measurements on phantoms by Nemec and Roth (1976) and Villafana *et al.* (1978) show that the dose to the orbits and skin of the patient can be high. A series of dose measurements similar to those made in the neurosurgical theatre was therefore undertaken.

Dosimeters were placed on the right and left temples and on the right orbit of the patient. Since in these examinations conscious patients were being asked to co-operate it was thought unreasonable to try to measure the dose to both orbits. In addition, a dosimeter was placed in the region of the gonads. Table III shows the doses recorded on 16 patients together with the number of scans per investigation. The apparent discrepancy in the dose per investigation can be explained by the variation of the position of the scans on the head. If the scans are all in the region of the orbits a high dose will be produced, but if most of the scans are further up the head the dose is reduced. These results are in good agreement with the phantom measurements already referred to. The dose to the right temple is higher than to the left because the scanner does not travel a full 360 deg arc. All the dosimeters in the region of the gonads recorded less than 10 mrem.

TABLE III

DOSES RECEIVED BY PATIENTS DURING EMI BRAIN SCAN INVESTIGATIONS

No. of Scans per patient	No. of patients	Average dose (rad)		
		Right Temporal	Left Temporal	Right Orbit
1	2	0.35	0.20	1.05
3	2	4.19	0.60	0.95
4	4	1.35	0.36	1.04
5	3	2.15	1.05	0.95
6	3	4.53	2.08	1.34
7	2	1.90	0.14	1.08

$^{99}\text{Tc}^{m}$ BRAIN SCANNING

The doses received from a $^{99}\text{Tc}^{m}$ brain scan are well documented (ICRP 17, 1969). The dose to the orbits is not quoted but has been assumed to be approximately the same as that to the brain. For a 10 mCi dose this is 60 mrad. Attempts to measure this dose accurately have proved difficult. Preliminary measurements using TLD chip dosimeters placed on the eyebrows of several patients for a period of six hours following the injection recorded between 25 and 30 mrad.

The doses received by the staff involved have been reported previously (Heaton and Brown, 1975). The dose of most interest, that to the fingers of the person injecting the technetium, is reduced in Aberdeen to below 25 mrad because the total load is spread among several doctors due to the number of wards involved.

CONCLUSIONS

Quite a large percentage of the patients undergoing neuroradiological investigations are subject to both types of X-ray examination. In the worst case this could involve a dose to the right eye in excess of 25 rad and similar doses to the surrounding skin. These doses are high and if at all possible should be reduced by using eye shields during cerebral angiography.

The population gonad dose from these investigations is negligible. The dose from scanning with $^{99}\text{Tc}^{m}$ does not add much to that from the X-ray examinations and does not alter the population gonad dose.

As has been shown, the dose to the fingers of radiologists carrying out cerebral angiographic procedures could be as high as 7.5 rad per year taking the average dose per examination as 15 mrad for a work load of ten examinations per week. Although this is only one tenth of the present maximum permitted dose equivalent of 75 rem per year it is a somewhat higher fraction of the limit proposed in ICRP 26 of 50 rem. In practice, each radiologist would receive a lower total dose during cerebral angiography procedures because of the rotation of staff and the lower number of examinations probably required. However, in a busy department this dose cannot be neglected and efforts should be made to reduce it as much as possible by effective methods such as the considerable reduction achieved by the use of a protective lead-rubber panel between the patient's head and the radiologist.

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Book reviews

Third International Symposium on Orbital Disorders. Edited by Orbital Centre of the Amsterdam University Eye Hospital, The Netherland Ophthalmic Research Institute, The Netherlands Ophthalmological Society, The New York Eye and Ear Infirmary. pp. xviii + 546, 1978 (Dr. W. Jung, bv. Publishers, The Hague/Boston/London) Dutch Guilders 175.00/$87.50.

ISBN 90–6193–570–9

This book contains the edited papers of an International Symposium which took place in September, 1977. The presentation covered most aspects of diagnosis and therapy including reconstructive surgery and radiotherapy.

Much original work is presented and most of the papers are of high standard. The majority of the radiological papers deal with ultrasonography and computed tomography, though there are a few excellent papers on orbital venography and carotid angiography and on comparisons between the results of the various techniques. Inevitably there is some overlap in the contributions, but good editing has kept this down to reasonable proportions.

The majority of the contributions are published in full, but it is unfortunate that references are omitted from others and it is especially frustrating to find only short abstracts of some presentations without any indication of whether the material has been published elsewhere. Most of the illustrations are good; some are of poor quality, but all are adequate to show the lesion being described.

The book is well produced and nicely bound. It is unfortunate that the delay in publication has involved a period during which high resolution scanning has become available, so that some of the computed tomograms are of poorer quality than those now obtainable. However, virtually all the text is still relevant to neuroradiologists and other interested in orbital diseases.

B. E. Kendall.

Handbook of Clinical Ultrasound. By M. de Vlieger, J. H. Holmes, E. Kazner, G. Kossoff, A. Kratochwil, R. Kraus, J. Poujol and D. M. Strandness, pp. xviii + 970, incl. index, 1978 (Chichester, Sussex; John Wiley & Sons Ltd.) £42·50.

ISBN 0–471–02744–8

This "handbook" is a large textbook of over 900 pages produced by 95 contributors controlled by eight editors. Clearly there are many variations of style and presentation. The illustrations are mixed with some black on white and others white on black. This does not worry me particularly as many journals have no standardized method of presentation but some readers may find it irritating and some novices may be confused. Although some sections have good quality grey scale illustrations I was very disappointed at the large number of bistable pictures. This probably reflects the time taken to publish such a text.

The contents are widely based with interesting sections on the history of ultrasound as well as clearly written chapters on the basic physics. Obstetrics and gynaecology are fairly well dealt with but not in such depth as some texts devoted to these subjects. The chapter on fetal abnormalities is limited mainly to neurological defects but there is an interesting section on fetal physiology.

The chapter on the pancreas is very brief and superficial but this is balanced by an excellent series of chapters on echocardiography understandable by novices. There are good articles on the use of Doppler ultrasound and on ophthalmological ultrasound applications. The 160 pages devoted to the use of ultrasound in neurology are in my opinion a desperate overkill.

In many respects this textbook is a mixed bag and it is difficult to give it an overall recommendation but training centres will find it useful.

A. B. Ayers.

1979, *British Journal of Radiology*, 52, 893–896 NOVEMBER 1979

Cytotoxicity of misonidazole *in vivo* under conditions of prolonged contact of drug with the tumour cells

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(*Received February 1979*)

ABSTRACT

A single high dose of misonidazole ($\geqslant 1$ mg/g) given to BALB/c mice bearing EMT6 tumours kills approximately 90% of the tumour cells. No cytotoxicity, however, can be demonstrated at more clinically relevant dose levels ($\leqslant 0.3$ mg/g). However, Stratford and Adams (1978) have shown that extensive killing of hypoxic cells occurs *in vitro* with low concentrations of misonidazole provided that the contact time is long, such as would occur in man in whom the plasma half-life of misonidazole is approximately 12 hours.

We have attempted to simulate the human situation in the BALB/c mouse by performing bilateral kidney ligations prior to injection of misonidazole. This extends the apparent plasma half-life of misonidazole plus its O-demethylated metabolite after an injection of 0.1 mg/g of misonidazole from approximately one hour to seven hours. This provided a good fit over the first nine hours to the *in vitro* simulation of the human plasma clearance curve done by Stratford and Adams (1978). However, despite finding extensive killing of tumour cells at the high dose of misonidazole of 1.2 mg/g, no detectable cytotoxicity was observed in the low dose (0.1 mg/g) mice in which the plasma half-life had been extended to seven hours. This suggests that misonidazole will produce little, if any, cytotoxicity to human tumours.

Besides radiosensitizing hypoxic tumour cells *in vivo*, the electron affinic radiosensitizer, misonidazole, is also toxic to cells under hypoxic conditions. This has been shown to occur *in vitro* (Hall and Roizin-Towle, 1975; Moore *et al.*, 1976; Sridhar *et al.*, 1976), and in several mouse tumours *in vivo*, albeit to a smaller extent than the degree of radiosensitization produced (Sheldon and Hill, 1977). In fact, however, the cytotoxicity does not only affect hypoxic cells, but kills both oxygenated and hypoxic cells in a situation where both are present (Brown, 1977; Olive and Durand, 1978). This is consistent with the finding that under hypoxic conditions metabolites of misonidazole are produced which are toxic to mammalian cells irrespective of their state of oxygenation (Wong *et al.*, 1978).

The fact that this cytotoxicity occurs *in vitro* at drug levels which can be reached in human tumours has led to the hope that it might be of clinical importance. It has also been pointed out that because the cytotoxicity depends on extended contact of the drug with hypoxic cells, the short half-life of misonidazole in the mouse would tend to minimize the extent of killing of hypoxic cells in mouse tumours and hence underestimate the clinical potential of this cytotoxicity (Denekamp and Fowler, 1978). This has been well demonstrated by Stratford and Adams (1978) who simulated *in vitro* the half-life of misonidazole in mouse and man by continuous dilution of the hypoxic medium with half-times of one and 12 hours respectively. They showed that if the initial concentration of misonidazole was 5 mM (1000 μg/ml) and the half-time was one hour, the level of cell killing of the hypoxic cells at 12–18 hours was much less than if the initial concentration was 10-fold lower (0.5 mM) and the half-life 12 hours. They concluded that misonidazole-induced toxicity to hypoxic cells may well contribute to overall radiosensitization in man to an extent much greater than has been seen in the mouse.

It seemed feasible to test this conclusion in the mouse by artificially extending the plasma half-life of misonidazole from one to two hours to a half-life comparable to that in man. This was done by ligation of both kidneys approximately two hours before injection of the drug. This prevents all renal excretion, and limits the loss of misonidazole and its O-demethylated metabolite (Ro-05-9963) in the plasma to metabolism alone, extending the half-life (of misonidazole plus Ro-05-9963) from two hours to approximately ten hours after a single dose of 5 mM/kg (1 mg/g) (Brown *et al.*, 1979).

METHOD

BALB/c mice, bearing EMT6/St/lu tumours of approximately 6 mm mean diameter, were either untreated, received double kidney ligation ("nephrectomy"), or were sham-operated, prior to an injection of either saline or misonidazole at a concentration of 0.1 mg/g or 1.2 mg/g (the latter concentration to control groups only). The mice were then killed either immediately or at 8, 16, or 24 hours after injection, the tumours pooled (four per group) and weighed, and single-cell suspensions prepared and plated for colony formation as described previously (Brown, 1977). This enabled the total number of clonogenic cells extracted per g of tumour to be calculated for each group. Plasma and tumour samples were also taken at these time intervals for analysis of misonidazole and Ro-05-9963 concentration by high-performance liquid chromatography (Brown *et al.*, 1979).

Results

It is apparent from the results of this experiment (Fig. 1) and from the previously published data, also plotted, that although there is ample evidence for cytotoxicity to the tumour cells at the high doses of misonidazole (1.0 and 1.2 mg/g), there is no detectable cell killing at the lower dose of 0.1 mg/g whether or not the half-life of the drug was prolonged by kidney ligation. Plasma levels in the four groups are shown in Table I and in Fig. 2. Also shown in Fig. 2 is the simulation of the misonidazole half-life in man obtained *in vitro* by Stratford and Adams (1978) for which they demonstrated extensive hypoxic cell killing. Tumour levels in the various groups mostly reflected plasma levels, and in the "nephrectomy" group the tumour/plasma ratio was 0.60±0.03 (range 0.50 to 0.70).

Discussion

The question of why the *in vivo* tumour data are in direct conflict with the results obtained by Stratford and Adams (1978) using hypoxic cells *in vitro* cannot be answered definitively. One possibility is that the shorter half-life in the nephrectomized mice (seven hours) compared with that in the *in vitro* experiment (12 hours), plus the fact that the actual tumour concentration was only 60% of that in the plasma, might together have reduced the cytotoxicity to negligible levels. However, the measured plasma levels up to nine hours match the *in vitro* experiment very well, and by this time the cytotoxicity found by Stratford and Adams (1978) in the low concentration group was equal to the maximum observed in the high concentration group. The lower tumour concentration, however, remains a possible, if unlikely, explanation of the difference.

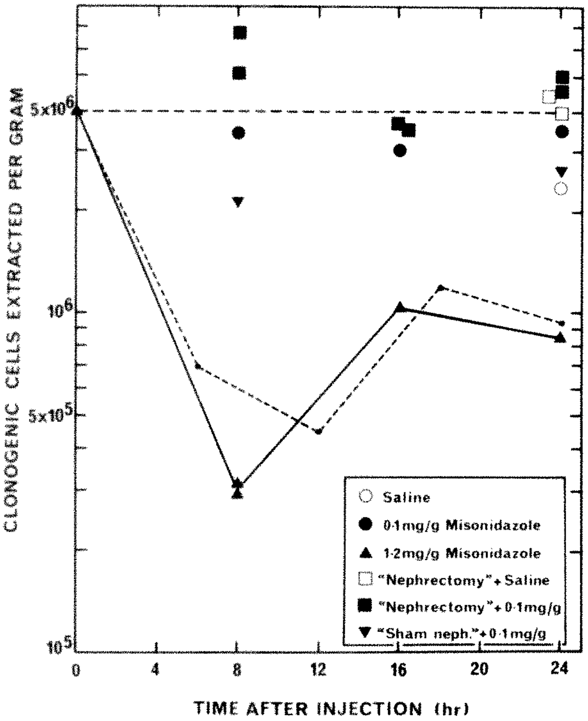

Fig. 1.

The number of clonogenic cells extracted per g of EMT6/St/lu tumours as a function of time after injection of misonidazole. Each point was obtained from four pooled tumours. The lower dotted line shows previously published data for the injection of 1.0 mg/g misonidazole (Brown, 1977).

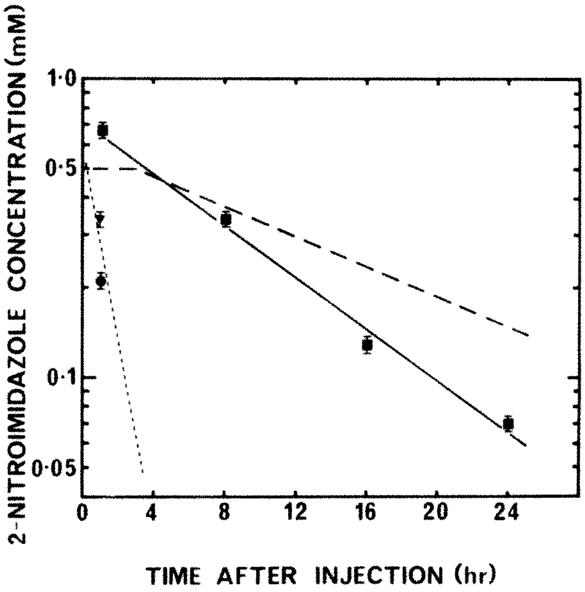

Fig. 2.

The concentration of misonidazole+Ro-05-9963 in the plasma as a function of time after injection of 0.5 mmol/kg (0.1 mg/g) of misonidazole into "nephrectomized" mice (■), sham-operated mice (▼), or untreated controls (●). The dashed line shows the variation of concentration of misonidazole achieved by Stratford and Adams (1978) in their "12 hour half-life" *in vitro* experiment. The dotted line drawn through the non-nephrectomized data has a half-life of one hour (the half-life of misonidazole after an injection of 0.1 mg/g). The line through the nephrectomy data was fitted by least squares regression analysis and gives a half-life of misonidazole+Ro-05-9963 of 6.9±0.2 hours.

However, we believe that the most likely explanation is that it is a result of the different rates of killing of chronically hypoxic cells under the two conditions. From the data of Stratford and Adams (1978) it can be seen that a high concentration of misonidazole (5 mM) reduces the surviving fraction of hypoxic cells to 10% by two and a half hours after the beginning of exposure, whereas the low concentration (0.5 mM) coupled with a long dilution half-life requires six hours of exposure to reduce the survival to this level. Thus, in the mouse with high doses and a short plasma half-life, significant cytotoxicity and the build up of cytotoxic metabolites would occur within two to three hours of injection. On the other hand, if the dose is low and the plasma half-life is 12 hours, the same cytotoxicity would require six hours to develop, and this is probably longer than the natural survival time of the chronically hypoxic cells (Franko and Sutherland, 1978; Hirst and Denekamp, 1979). Thus, no additional cytotoxicity to the chronically hypoxic cells would be produced.

A further problem with misonidazole as a cytotoxic agent is that even if it killed all the chronically hypoxic cells it would not be expected to be effective against acutely hypoxic cells—*i.e.* cells which have become hypoxic due to the periodic stopping and starting of blood flow in individual tumour vessels (Brown, 1979; Reinhold, *et al.* 1977).

Since the peak plasma concentration of misonidazole that was achieved in the mice with ligated kidneys (0.67 mM or 135 μg/ml) is about the highest that one might expect to obtain clinically, and the half-life in these mice was within the human range, the present data argue against cytotoxicity contributing to the radiosensitizing effect of misonidazole in human tumours. This is consistent with the analysis by Denekamp and McNally (1978) of the data of Thomlinson *et al.* (1976) who showed radiosensitization of one nodule from a cervix carcinoma in relation to another in the same misonidazole-treated patient.

Thus, it would appear that unless the cytotoxicity can be significantly enhanced *in vivo*, the chief benefit of misonidazole for human patients will be its ability to radiosensitize rather than kill the hypoxic cells in the tumours. In this regard, it will not be relevant whether these hypoxic cells are acutely or chronically hypoxic (Brown, 1979).

ACKNOWLEDGMENTS

The authors are grateful for the technical assistance of Ms. R. Goddard and Mr. E. Parker and for helpful discussion with Professor N. M. Bleehen and Dr. P. Workman. This investigation was supported by Research Grant No. CA-15201 from the National Cancer Institute, DHEW, by the Medical Research Council, and by the International Union Against Cancer for their award of an American Cancer Society Eleanor Roosevelt International Cancer Fellowship (to JMB).

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TABLE I

PLASMA LEVELS OF TOTAL NON-CONJUGATED 2-NITROIMIDAZOLES (MISONIDAZOLE + RO–05–9963) AT DIFFERENT TIMES AFTER INJECTION

Treatment	Dose of misonidazole	Total non-conjugated 2-nitroimidazoles in plasma (mM)			
		1 hour	8 hours	16 hours	24 hours
Control	1.2 mg/g 0.1 mg/g	4.39 ± 0.42 0.21 ± 0.01	0.68 ± 0.14 < 0.05	< 0.05 < 0.05	< 0.005 < 0.005
"Nephrectomy"	0.1 mg/g	0.67 ± 0.04	0.34 ± 0.02	0.13 ± 0.01	0.07 ± 0.01
"Sham nephrectomy"	0.1 mg/g	0.34 ± 0.02	< 0.05	< 0.05	< 0.005

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Book reviews

Lehrbuch der Röntgendiagnostik. 5 parts. Vol. 2/part 1 edited by H. R. Schinz, W. E. Baensch, D. W. Frommhold, R. Glauner, E. Uehlinger and J. Wellauer. 6th edition, 1979, pp. xvi + 1128 (Georg Thieme Verlag, Stuttgart) DM 580.

ISBN 3–13–3952–06–4.

We are told in the preface that the first volumes of this edition were published in 1965 and that the end of this edition is now at last in sight. Unfortunately, we are not told how many parts there will be in total and how the material is subdivided among them. However, judging from this text, a radiologist interested in the skeleton would at least have to purchase Volume II part 2 and also Volume I. This means an expenditure of several hundred pounds without the certainty even then of having a complete textbook of skeletal radiology.

There are very good chapters on infections of bones and joints, inflammatory joint disease, degenerative joint disease, sarcoidosis of bone, TB, metabolic bone disease and the effects of hormones, circulatory disturbance and physical factors on bone. Fibrous dysplasia and Pagets disease are well described.

There is a useful chapter on isotope scanning of bone and also a chapter on bone densitometry.

The chapter on normal bone variants is poor and in no way compares with other texts on this subject. The chapter on fractures is overwhelmed by details of wires, nails, plates and operative techniques more suitable for orthopaedic surgeons while failing to stress the important fractures from the radiologists point of view. I could not find a discussion of scaphoid fractures of the wrist or a mention of avascular necrosis of the talus. Radiographic techniques in diagnosis of fractures are not discussed.

The chapter on arthrography is incomplete in its description and refers you to Volume I.

Bone dysplasias get a very cursory mention and one hopes will get the treatment they deserve in another volume.

Although the book has very good sections, the total result is unbalanced and incomplete. The casualty officer or trainee trying to decide whether the X-ray is normal will find little help here. I suspect that the radiologist interested in children will have to look somewhere else even after purchasing part 2 of Volume I. There are better, more convenient and cheaper sources of the information contained in this volume.

G. M. STEINER.

Nuclear Medicine in Urology and Nephrology. By P. H. O'Reilly, R. A. Shields and H. J. Testa, pp. xiii + 201, 1979 (Butterworth, London/Boston), £15·50.

ISBN 0–407–00151–4

This book is an example of a welcome trend to set out critically and in depth the application of nuclear medicine in a particular clinical field, and to discuss its value in relation to other diagnostic methods.

The first part describes the radionuclide procedures relevant to urology in a clear manner which will be useful to clinicians unfamiliar with these techniques. There follow seven chapters dealing systematically with clinical applications including ureteric obstruction, focal renal abnormalities, hypertension and renal failure, congenital abnormalities, trauma and renal transplant assessment. This section makes a brave attempt to be both comprehensive and concise, and generally succeeds. While some urologists may find the discussion of controversial clinical aspects to be somewhat superficial in places, a compelling case is presented that radionuclide studies should be much more widely used, both to obtain additional information and in some cases to reduce the need for conventional radiological examinations which are often more invasive and involve higher radiation to the patient. The place of renal parenchymal imaging is perhaps overemphasized. Ultrasound, which receives only scant mention in comparison, is even less invasive and is more accurate in distinguishing between tumours and cysts.

The final part of the book deals very competently with the physics and technical aspects of the subject including instrumentation, radiopharmaceuticals and radiation dosimetry. The mathematical chapter contains a lucid explanation of the important technique of deconvolution.

The whole book is well illustrated although in some scintigrams an arrow indicating the exact position of the abnormality would be informative to those unfamiliar with this type of image. One must also take exception to the inappropriate use of the terms AP and PA projection (*e.g.* pp. 17, 41, 68, 92, 111) in connection with scintigrams.

This book will be of interest to all clinicians involved in the management of renal disease and should be available in all departments offering a diagnostic radionuclide service.

E. P. WRAIGHT.

1979, *British Journal of Radiology*, *52*, 897–899

Case reports

Polycystic liver and other hepatic masses mimicking gall-bladder disease

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(*Received August 1978 and in revised form March 1979*)

Hepatic and biliary tract diseases can both present as pain or mass in the right upper quadrant of the abdomen. Occasionally, hepatic masses impress the gall-bladder, simulating gall-bladder disease both symptomatically and radiographically. Ultrasonography and computed tomography (CT) imaging have facilitated the preoperative differentiation between hepatic and biliary tract disease and, further, between cysts (polycystic liver disease) and solid tumours. We wish to report a patient with hepatic masses and review similar reports to illustrate that when filling defects are noted in the gall-bladder on the cholecystogram, hepatic disease can then be differentiated from biliary tract disease without the need for laparotomy.

CASE REPORT

A 45-year-old hypertensive woman was admitted to our hospital because of a six-month history of an enlarging abdominal mass and a sensation of pressure and fullness. She had no associated pain, jaundice, nausea, vomiting, or change in bowel habits.

Physical examination disclosed an enlarged, non-tender liver and discrete, mobile masses 8 to 12 cm in diameter in the mid epigastrium. Laboratory studies revealed no abnormalities.

An oral cholecystogram showed two large filling defects in the lateral aspect of the fundus of the gall-bladder (Fig. 1). An upper gastrointestinal series showed a mass impressing the duodenal bulb (Fig. 2). Excretory urography with tomography demonstrated numerous cysts of various sizes within the kidneys and liver (Fig. 3). Technetium 99m sulphur colloid scintiphotos showed an enlarged liver with multiple areas of diminished uptake (Fig. 4). Ultrasonographic examination of the liver (Fig. 5) and kidneys revealed that these areas of diminished uptake were sonolucent with strong through transmission consistent with multiple cysts. The cysts were separate from the gall-bladder.

The radiographic findings combined with those from ultrasonography and scintigraphy strongly indicated the diagnosis of polycystic liver and kidney disease. The patient was discharged without surgical intervention and has done well. Two years later, oral cholecystography, excretory urography, radionuclide scanning of the liver, and ultrasonography of the liver and kidneys demonstrated no change in findings.

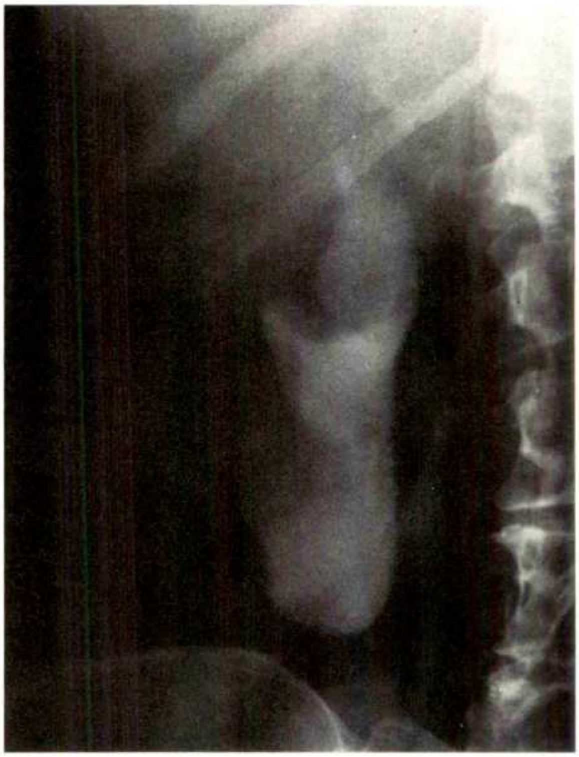

FIG. 1.

Oral cholecystogram showing round, filling defects in lateral aspect of the gall-bladder.

DISCUSSION

Several types of hepatic masses can cause filling defects in the gall-bladder on the oral cholecystogram (Fisher, 1968). Polycystic disease of the liver has been suspected to cause this effect in five of the cases reported (Fisher, 1968; Joffe and Babenco, 1974). Polycystic disease of the liver is frequently asymptomatic; however, one report (Comfort *et al.*, 1952) of 24 patients with polycystic disease of the liver or kidney, or both, showed that 13 patients had symptoms referable to the liver. Specific symptoms for these 13 patients were right upper quadrant mass, pressure or dull abdominal discomfort, needle-like right upper quadrant pain, and colicky abdominal pain (in one case accompanied by chills and fever). At surgery, none of the 13 patients was found to have gall-bladder disease.

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The similarity of the above symptoms to those of gall-bladder disease is obvious. Moreover, the age distribution of patients having polycystic disease of the liver is similar to that for patients with gall-bladder disease–both often first diagnosed when the patients are between the fifth and sixth decades of life (Sandy, 1965).

Other intrahepatic masses that impress the gall-bladder are solitary liver cyst, primary hepatoma, haemangioma, metastatic carcinoma (Joffe and Babenco, 1974), and hepar lobatum (due to tertiary syphillis) (Fisher, 1968). In patients with these diseases the presenting symptoms also frequently mimic gall-bladder disease. Fisher (1968) suggests that liver abscesses, liver granulomas, or liver lobulation due to scarring can also deform the gall-bladder.

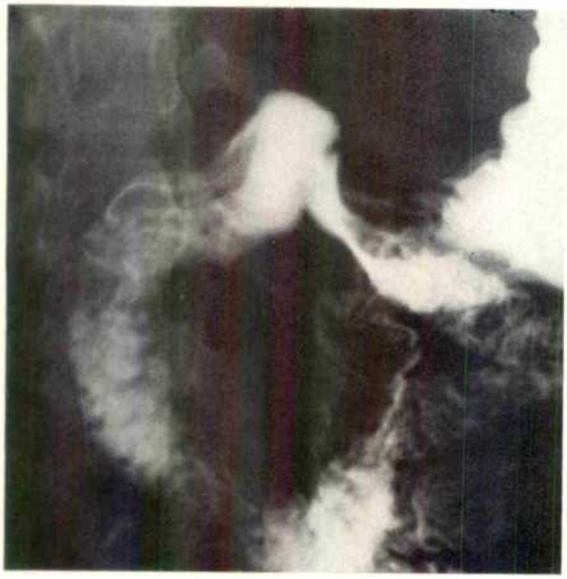

FIG. 2.

X-ray film from upper gastrointestinal series shows mass impression on superior aspect of the duodenal bulb and also extrinsic indentation on upper surface of pyloric antrum.

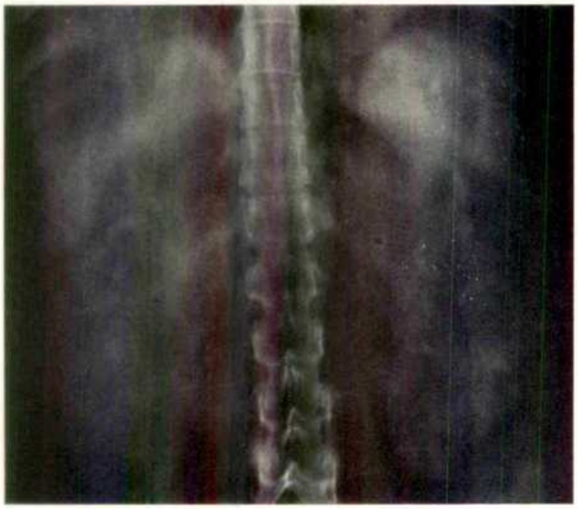

FIG. 3.

Nephrotomogram shows multiple cystic lesions in enlarged kidneys and liver.

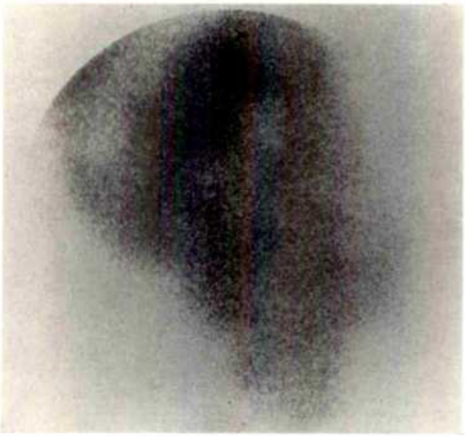

FIG. 4.

Right lateral liver scan using technetium-99m sulphur colloid showing enlarged liver with multiple areas of diminished uptake.

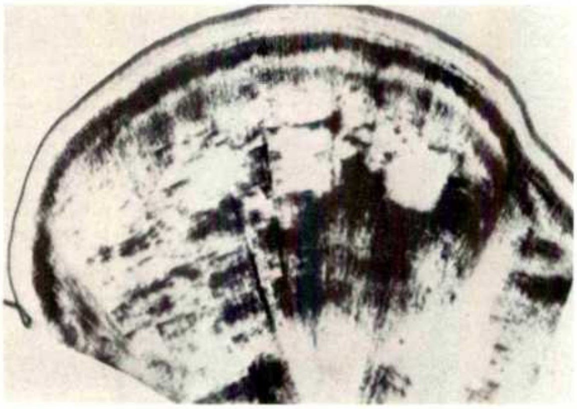

FIG. 5.

Transverse ultrasonogram of the liver at level of umbilicus +14 cm shows multiple cystic lesions with characteristic acoustical transmission.

Extrahepatic masses that can impress the gall-bladder include the duodenal bulb, distended colon, and peripheral lymph nodes (Fisher, 1968). Although impressions by bowel should not present a diagnostic problem, lymph nodes impressing the gall-bladder could produce radiographic findings that mimic intrinsic gall-bladder disease.

In the literature, we found 11 cases in which masses extrinsic to the gall-bladder produced radiographic findings that mimicked gall-bladder disease. The findings on the X-ray films of these reported patients (Comfort *et al.*, 1952; Fisher, 1968; Joffe and Babenco, 1974) consisted primarily of single or multiple filling defects in the gall-bladder on the cholecystogram. Although the filling defects usually changed in appearance with change in patient position, they remained fixed when the gall-bladder was adherent to the liver or intrahepatic in location. In addition to impressions upon the gall-bladder, other findings noted on X-ray films were displacement of the duodenum, stomach, or colon and elevation of the right hemidiaphragm by an enlarged liver (Geist, 1955).

As well as extrinsic compression of the gall-bladder, the differential diagnosis of filling defects of the type shown in our case noted on cholecystograms includes adenomyomatosis, intramural cyst or granuloma, and neoplasms (Joffe and Babenco, 1974).

Although Niemetz *et al.* suggested in 1949 that there are no radiographic signs characteristic of polycystic disease of the liver, cyst wall calcification has been considered to be highly suggestive of polycystic liver (Comfort *et al.*, 1952). The advent of imaging modalities such as ultrasonography and computed tomography (CT) has recently made possible preoperative diagnosis of polycystic disease of the liver in most cases (Igawa and Miyagishi, 1972; Taylor *et al.*, 1976). Ultrasound and CT body scanning are also extremely accurate in defining the nature of hepatic lesions (Alfidi *et al.*, 1976) and can often help differentiate hepatic from gall-bladder disease. In our patient, ultrasonograms demonstrated multiple fluid-filled cysts adjacent to the gall-bladder. Further diagnostic evaluation by means of excretory urography disclosed the classic radiographic appearance of polycystic kidney disease. It is particularly noteworthy that renal involvement in patients with polycystic liver disease occurs with only 50% frequency (Sandy, 1965); therefore, the excretory urogram often will not aid in the differential diagnosis. Ultrasound and CT body scanning should be able to obviate the need for laparotomy. Surgical treatment of polycystic disease of the liver is generally unsatisfactory, with cyst puncture offering only temporary relief from the patient's sense of weight or pressure in the abdomen. The diffuse distribution of cysts in the liver makes attempts at radical surgical treatment unfeasible in most instances (Comfort *et al.*, 1952).

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The ultrasound appearance of subdiaphragmatic rupture of a right lobe liver abscess in a two-year-old child

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(*Received May 1979*)

Amoebic liver abscess is a common disease amongst the black population in the coastal region of Natal. All age groups may be affected and if diagnosed early and treated properly the disease carries a good prognosis (Adams and MacLeod, 1977). We use ultrasound routinely for diagnosis and for accurate aspiration therapy. We report here the ultrasound appearances of an amoebic liver abscess which ruptured into the subphrenic space. To our knowledge this has not previously been described.

CASE REPORT

A two-year-old black child, weight 9 kg, was admitted with a one week history of fever, vomiting and passage of loose stools. On admission her temperature was 36.7°C and pulse 120 per minute. There were crepitations at the right base and the liver was enlarged and tender. Relevant investigations were: haemoglobin 7 g/dl, white cell count 7000/mm^3 (neutrophils 46%, lymphocytes 40%, eosinophils 1%), serum complement fixation test for ameobiasis positive, stools contained necrotic debris and mucous, but no blood. A chest radiograph (Fig. 1A) showed moderate elevation of the right diaphragm and linear actelectasis at the right base. Ultrasound examination of the liver (Fig. 1B) was performed in parasagittal sections with the patient lying supine. A 3.5 cm well defined transonic lesion was found lying posteriorly in the right lobe of the liver between the upper pole of the right kidney and the right hemidiaphragm. The features were those of a liver abscess, which was aspirated yielding 100 ml of brown pus. Oral metronidazole and systemic antibiotics were administered.

The patient developed a persistent pyrexia and the tender hepatomegaly failed to resolve. Five days after admission the radiological investigations were repeated. The chest radiograph (Fig. 2A) revealed two separate cavities containing air and fluid. The supero-lateral cavity was diagnosed as a subphrenic abscess and the infero-medial cavity as the liver abscess, which had ruptured. The ultrasound scan on the same day (Fig. 2B) supported these findings. Compared to the initial scan the liver abscess

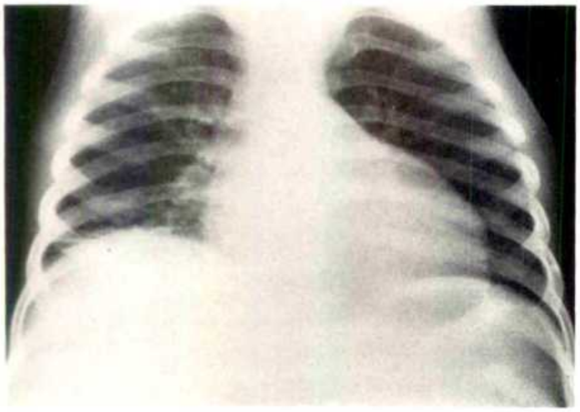

FIG. 1A.

Chest radiograph taken on admission shows some linear atelectasis at the right base and elevation of right hemidiaphragm.

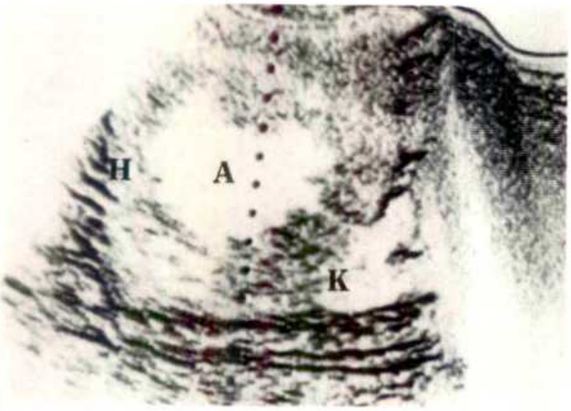

FIG. 1B.

Supine longitudinal parasagittal scan through the right lobe of the liver (L+4). A well defined 3.5 cm transonic area (A) is demonstrated. Note: normal hemidiaphragm and liver capsule combined interface (H) and upper pole of the right kidney (K).

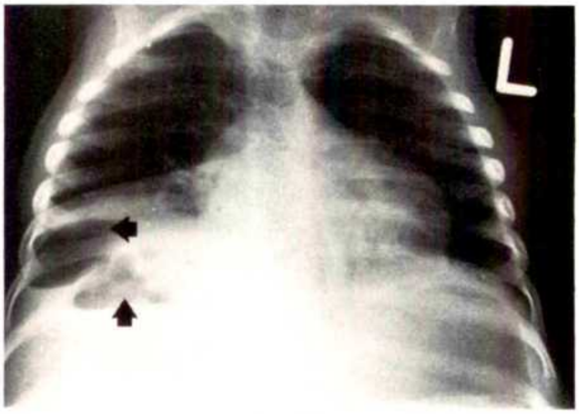

FIG. 2A.

Chest radiograph taken five days after Fig. 1A demonstrates subphrenic gas (horizontal arrow) and gas in the liver abscess (vertical arrow). There is some collapse and consolidation in the right lower lobe of the lung.

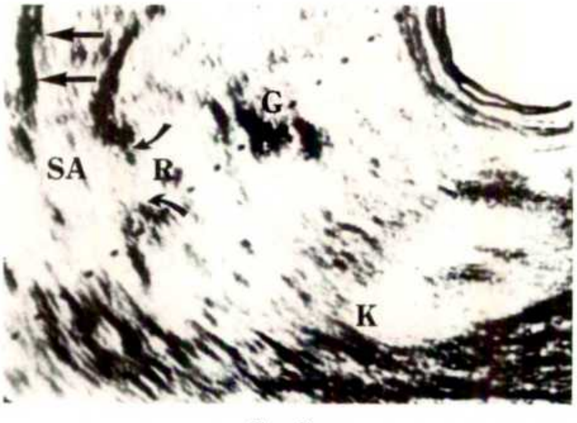

FIG. 2B.

Supine longitudinal parasagittal scan through the right lobe of the liver (L+4). Note that the well-defined lesion seen in Fig. 1B is now no longer present. The abscess wall is now ill-defined and there are irregular echoes within the abscess with very dense echoes superiorly. These are due to gas (G). The rupture (R) in the liver capsule (curved arrow) is demonstrated. The subphrenic abscess (SA) is seen between the interface of the right hemidiaphragm (straight arrows) and the ruptured liver capsule (curved arrows).

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cavity had enlarged and its walls were no longer well defined. The liver capsule was seen as a separate interface with a subphrenic collection of fluid between it and the hemidiaphragm. The presence of gas in the medially situated liver abscess led to some distortion of the ultrasonic characteristics.

Following ultrasonic confirmation of the diagnosis of ruptured liver abscess surgery was undertaken. The findings were an abscess in the postero-superior region of the right lobe of the liver, which had ruptured into the subphrenic space resulting in a localized collection of sero-purulent fluid. The right hemidiaphragm was intact. Intravenous metronidazole and systemic antibiotics were administered and there was progressive improvement in the patient's condition. Subsequent ultrasound scans demonstrated progressive resolution of the liver abscess, and the interface between the liver and hemidiaphragm returned to normal.

COMMENT

Plain film radiography of the chest and abdomen is useful in the diagnosis of amoebic liver abscess by showing elevation and reduced movement of the diaphragm, pleural effusion, lung collapse or consolidation and lung abscess (Rowland, 1963). Contrast radiography using air (Rao *et al.*, 1973) or micropaque barium sulphate (Bhasin *et al.*, 1977), have been used to assess the size and position of the abscess, but these are invasive and time-consuming procedures. Radioisotope scans define an abscess as a cold area within the liver in a high percentage of cases (Cuaron and Gordon, 1970), but do not distinguish cystic from solid lesions. The ultrasound appearances of amoebic liver abscesses have been described as areas devoid of echoes surrounded by normal liver (Ross, 1974) which can be located very accurately prior to aspiration (Vicary *et al.*, 1977).

The changing ultrasound appearance in our case considerably aided the pre-operative diagnosis of rupture of an amoebic liver abscess into the subdiaphragmatic space, thus expediting operation. The main feature on ultrasound scan was the appearance of the liver capsule as a separate interface from the diaphragm, once the abscess had ruptured.

The value of the chest radiograph immediately prior to ultrasound examination is stressed, as the presence of gas in the liver abscess may confuse the ultrasound interpretation by producing bizarre echoes.

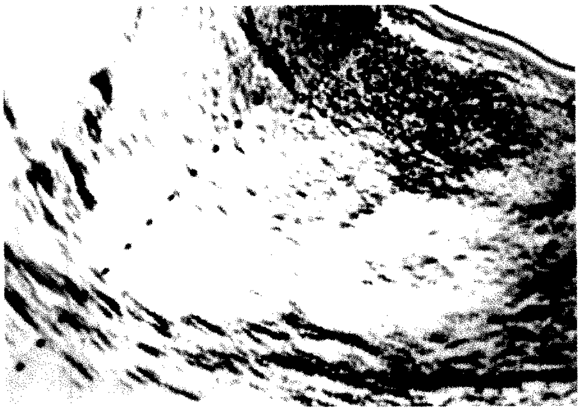

FIG. 3.

Longitudinal scan (L+4) demonstrating the liver echo pattern returning to normal. The combined interface of the liver and hemidiaphragm is now defined and intact.

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Posterior longitudinal ligament calcification of the cervical spine

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Calcification of the posterior longitudinal ligament in the cervical canal is an apparently rare phenomenon and amongst the reported cases is an almost exclusively Japanese disease. No case has previously been reported from the United Kingdom. The principal clinical and radiological features are reviewed. The value of computerized tomography in the diagnosis is illustrated.

CASE HISTORY

A Caucasian male, aged 58, presented with a two-year history of pain in the neck radiating down the outer aspect of both arms to the finger tips. There was numbness in the hands preventing the patient from performing some manual tasks and, in particular, interfering with his favourite pastime, fishing. Pain was accentuated by rotatory movements of the cervical spine. There was no relevant family or past medical history. In particular there was no history of previous neck trauma.

On examination there was total absence of the upper limb reflexes but no other neurological abnormality. All other systems were normal.

RADIOLOGICAL FEATURES

Plain films of the cervical spine from 1976 to 1978 were available for review. There was a dense band of calcific density from the lower border of the second to the lower border of the fourth cervical vertebra increasing from 3 to 4 mm in width over the two-year period (Fig. 1). The band of opacification was widest adjacent to the C2/3 intervertebral disc space. The normal cervical lordosis was lost. There was generalized disc space narrowing particularly between C5 and 7 with well-marked anterior and posterior osteophytes at these lower levels. The sagittal dimensions of the neural canal were narrow, being reduced to 12 mm at C7. Films in flexion and extension revealed exaggerated movement between the occiput and C2. There was no evidence of mobility at the level of the calcification, and markedly reduced movement below this level.

Tomography confirmed these features and showed no other evidence of abnormal calcification (Fig. 2).

CT scans confirmed the position of the calcification within the neural canal (Fig. 3). The width of the lesion was slightly greater to the right and in total occupied up to one-third of the sagittal and transverse dimensions of the canal.

Cervical myelography

Myodil flowed freely to the C4/5 disc space where there was a well-marked indentation from the degenerative spondylosis (Fig. 4). Less-marked changes were present between C5 and 7. Myodil then flowed freely into the basal cisterns in the prone and supine positions along the lateral recesses.

A Cloward fusion at C4/5 with a local decompression were offered, and declined.

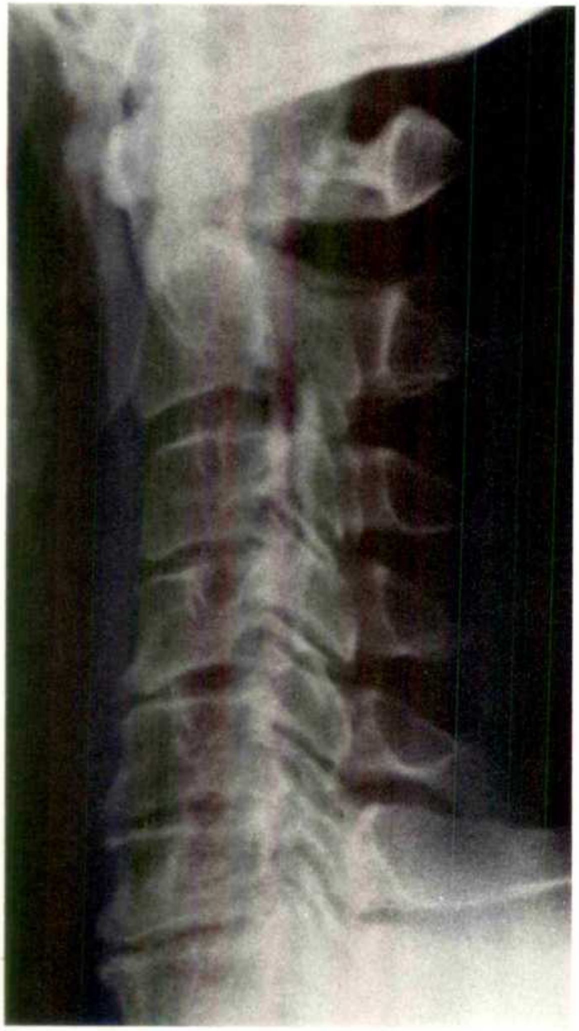

FIG. 1.

Lateral view of the cervical spine (1978). There is homogeneous calcification from the lower border of CV2 to the lower border of CV4. Degenerative disease maximally at CV4–7 and a shallow neural canal are also shown.

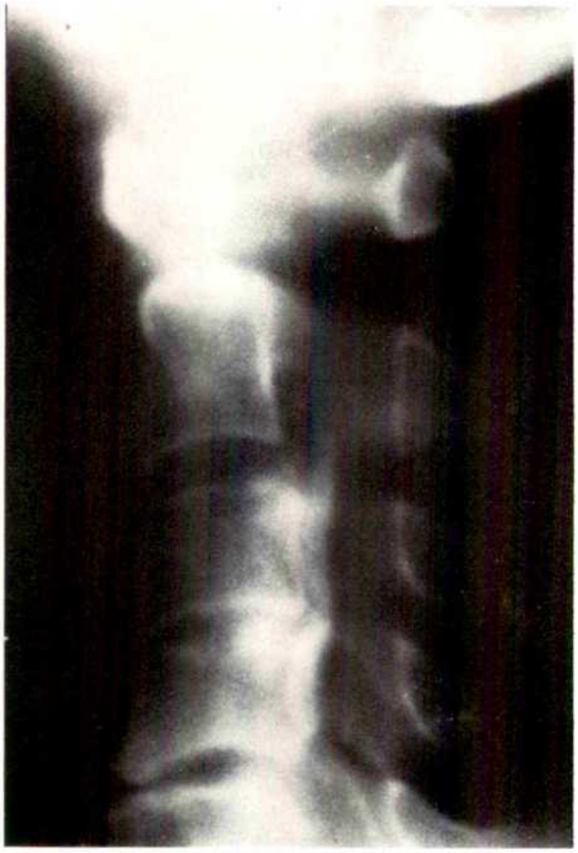

FIG. 2.

Lateral tomogram of cervical spine. The calcification is shown to lie in the mid-line.

DISCUSSION

Calcification or ossification of the posterior longitudinal ligament has been described as a cause of cervical myelopathy in Japanese (Hiramatsu and Noebechi, 1971; Onji *et al.*, 1967; Suzuki *et al.*, 1962; Terayama *et al.*, 1962; Yokoi, 1963), but this has been described previously in only three Caucasian patients (Minagi and Gronner, 1969; Palacios *et al.*, 1971) and one Arab (Christie, 1977).

In total 29 cases are available for review in the English literature (Hiramatsu and Nobechi, 1971; Minagi and Gronner, 1969; Onji *et al.*, 1967; Palacios *et al.*, 1971).

The age range is between 42 and 75 years of age, the mean age being 54 years. In these 29 cases there was an equal sex distribution (15 females: 14 males).

Calcification most commonly presents between C2 and C4 but may extend as far as C1 proximally and C7 distally. The calcification is usually dense and uniform. The thickness varies from paper-thin to 5 mm, often with slight narrowing adjacent to disc spaces.

The condition should not be confused with other calcifying and ossifying lesions of the spine, such as ankylosing spondylitis, senile hyperostosis and degenerative disease (Onji *et al.*, 1967). Generalized ligamentous calcification may be a feature of endemic fluorosis, but classically affects the ligamentum flavum (Singh *et al.*, 1962). Calcification of the anterior longitudinal ligament and intervertebral discs may be seen in acromegaly (Epstein, 1976). There is no evidence to suggest that it is a condition similar to the acute tendinitis recognized anterior to the spine in the longus colli (Newmark *et al.*, 1978). However, a recent report suggests that it may be a feature of diffuse idiopathic skeletal hyperostosis (DISH) occurring in as many as 50% of such cases (Resnick *et al.*, 1978). The present case has a developmentally narrow canal, a feature that has not been previously described in this condition.

The prevalence of this abnormality amongst

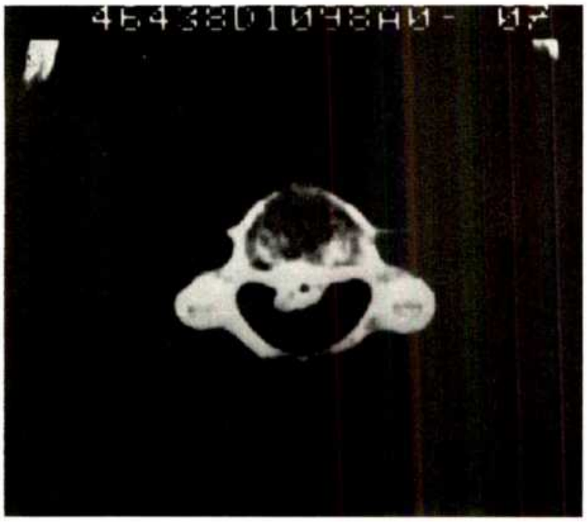

FIG. 3.

CT scans at the level of CV3. The calcification is shown anteriorly in the neural canal, rather wider to the right. A small zone of lucency is present between it and the posterior cortex of the vertebral body.

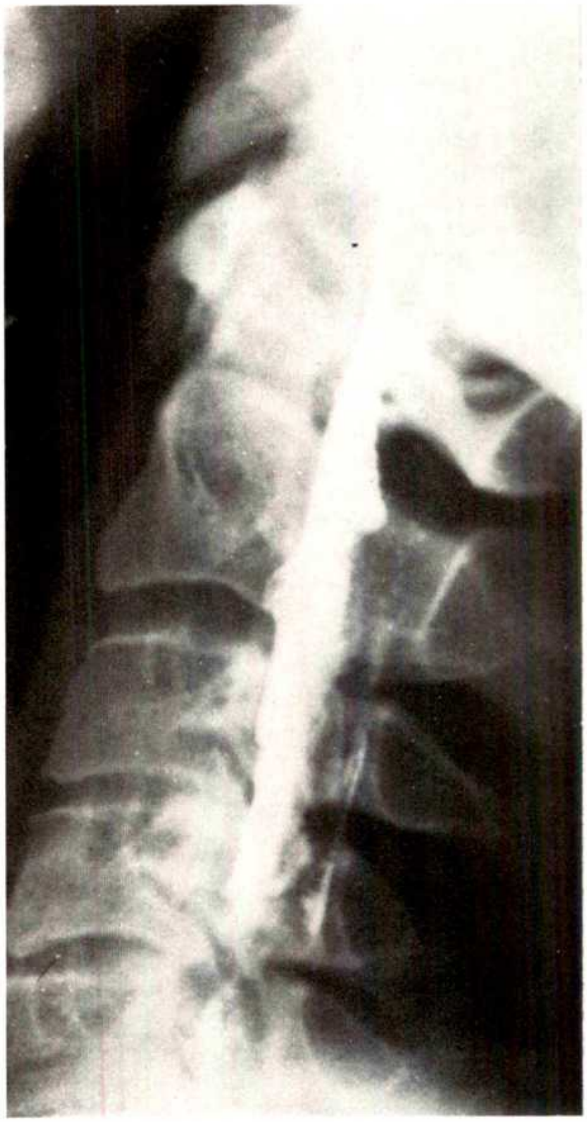

FIG. 4.

Cervical myelogram. lateral view. There is well-marked indentation of the myodil column at C4–5 due to degenerative disease. Myodil flows freely along the lateral recesses at the level of the posterior ligament calcification.

Japanese presenting with cervical spinal disorders and neurological symptoms has varied between 1% (Yokoi, 1963), and 1.7% (Onji *et al.*, 1967). However other authorities have found no such calcification in personal reviews of 1000 patients with cervical spine diseases even though 50% of their patients were of Japanese ancestry (Cloward cited by Onji *et al.*, 1967).

Cases previously examined at operation or autopsy have confirmed calcification and/or ossification in the posterior longitudinal ligament. Bone marrow production has also sometimes been seen. (Onji *et al.*, 1967; Palacios *et al.*, 1971; Terayama *et al.*, 1962). Onji *et al.* (1967) described two cases who at operation had the dura mater opened; this was highly adherent in the region of ossification and the protuberant ossified mass compressed the spinal cord. Histological examination of the specimens of ossified mass obtained by biopsy revealed different stages of ectopic bone formation from unorganized calcification to true bone. Terayama *et al.* (1962) described an autopsy finding demonstrating a gap between the ossification and the posterior wall of the vertebrae at some levels but absence of a gap at other levels (Fig. 3). Histological examination showed a thin layer of fibrous tissue overlying the ossification which was a part of the posterior longitudinal ligament.

The clinical findings have been attributed either to direct pressure by the calcified mass upon the spinal cord or compression of the anterior spinal arteries. The thickness of the calcified ligaments is found to correlate with the severity of symptoms in most patients (Onji *et al.*, 1967). The main presenting complaint is hand numbness (18 patients), the next most common symptom being difficulty in walking with a demonstrable spastic gait (13 patients). Other presentations include pain in the neck, shoulder and upper limb, and weakness of the lower limbs when an upper motor neurone lesion was invariable. Duration of symptoms varies from three months to 20 years. Physical examination reveals usually a slight reduction in light touch and pin-prick sense in the lower cervical dermatomes. In nearly half of patients the upper limit of reduced sensation does not correlate exactly with the level of calcification. In half the patients the tendon reflexes are exaggerated. Myelography usually reveals a narrowed cervical canal especially at the level of C3/4 where the calcification is usually at its greatest. In those patients where calcification is restricted to one or two segments, the symptoms as in the present case, are usually less marked, the patients complaining usually of mild numbness in the hands with no long tract signs.

Many of the reported symptomatic patients have no abnormality of the cervical vertebrae and the disc spaces are usually preserved. However, when degenerative features are demonstrated, as in the present case, differentiation between the symptoms caused by the calcified ligament and those due to the degenerative spondylosis may present great difficulty.

The aetiology of the condition is unknown. No consistent predisposing factor has been revealed and trauma was recorded in only four of the 29 cases. In each case a road traffic accident of unspecified severity had precipitated symptoms and had led to the identification of posterior longitudinal ligament calcification after the accident in at least two of the four cases.

Radiological assessment is usually straightforward but prognosis may be related to the cross-sectional area of the lesion relative to the neural canal. Axial transverse tomography has therefore been advocated as an important method of assessment (Hanai *et al.*, 1977). No previously reported case has been demonstrated by computerized tomography.

Management of the condition is surgical. A laminectomy and decompression are usually curative.

Acknowledgments

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Delayed radiation necrosis of a spinal nerve root presenting as an intra-spinal mass

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Frequently the nervous system is exposed to appreciable doses of radiation when a lesion within or in close proximity to the brain, spinal cord or peripheral nerves is the target of radiation therapy (Fischer and Holfelder, 1930; Kramer, 1968; Kramer *et al.*, 1972; Crompton and Layton, 1961; Stevenson and Eckhardt, 1945; Dynes and Smedal, 1960). Radiation induced necrosis of the central nervous system (CNS) is a well-recognized hazard (Fischer and Holfelder, 1930; Kramer, 1968; Kramer *et al.*, 1972; Crompton and Layton, 1961; Stevenson and Eckhardt, 1945; Dynes and Smedal, 1960). The site and extent correlates with zones of high radiation on dose reconstruction plans (Mikhael, 1978; 1979). Recognition of these post-radiation changes is important since surgical removal may significantly remove their neurological effects (Mikhael, 1978; 1979).

CASE REPORT

A 16-year-old male presented with a six-week history of progressive weakness of the arms and legs particularly on the left side. He had been treated for Hodgkin's disease (stage II–A) that presented as a left neck mass at the age of eight years. He received 4000 rad tumour dose (20 fractions over 40 days, 200 rad/day using 2 MeV X rays) (Fig. 3A). Approximately eight months later he was treated for right tonsillar recurrence. He received an additional 4000 rad tumour dose (20 fractions over 37 days using 15 MeV electron beam) to the neck area (Fig. 3B). His current complaints started seven years after the last course of therapy.

On physical examination there was no lymphadenopathy anywhere in the body. The patient could walk with an unsteady gait. Proprioception and vibration sense were decreased on the left side.

Craniocervical radiological examination showed well-defined destruction of the lateral mass of C_2–C_3 on the left side with no evidence of newly formed bone at the site of destruction (Fig. 1). A cervical myelogram showed a well-defined lobulated intradural extramedullary mass opposite C_1–C_2–C_3 on the left side with a posterolateral extradural component (Fig. 2A, B, C). The differential diagnosis of the mass included meningioma, neurofibroma and less likely recurrent Hodgkin's disease, since the usual type of spinal involvement in lymphoma is extradural (Shapiro, 1975).

The patient underwent cervical laminectomy of C_1–C_2–C_3 and a lateral hard fibrotic mass was seen mainly in the intradural extramedullary space with an extradural posterolateral extension. The mass was extremely tough and

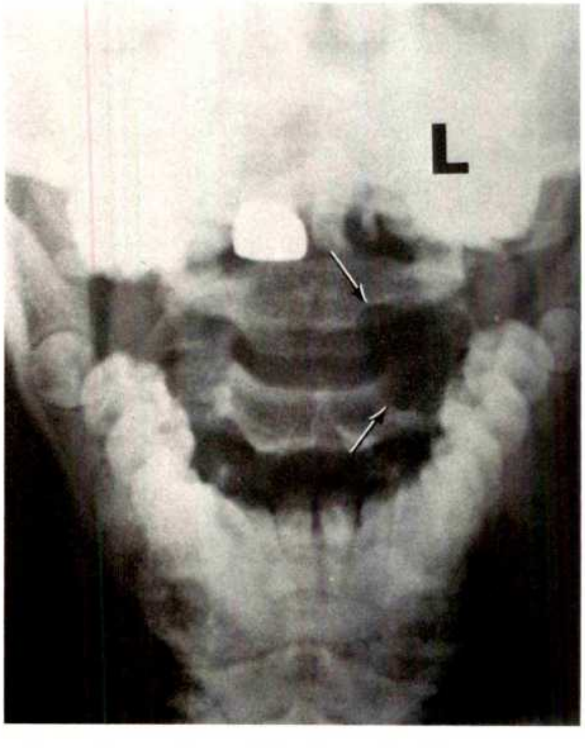
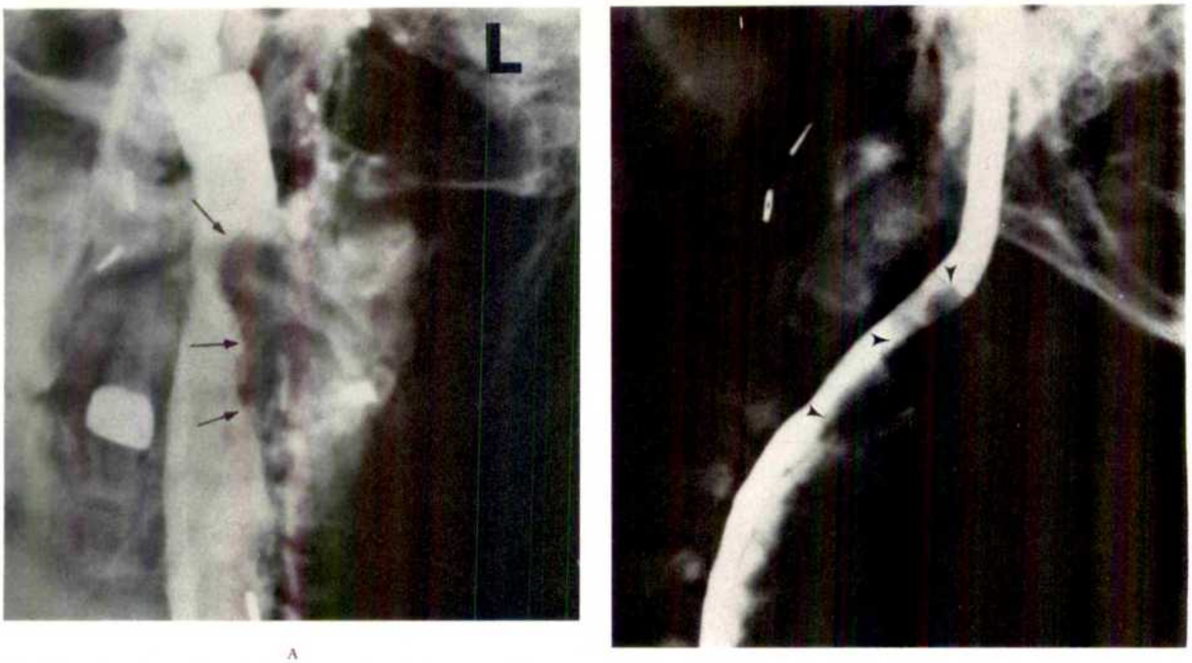


FIG. 1.

X-ray of the upper cervical spine (frontal view) showing a well-demarcated destruction of the lateral mass of C_2 and C_3 on the left side (arrows).

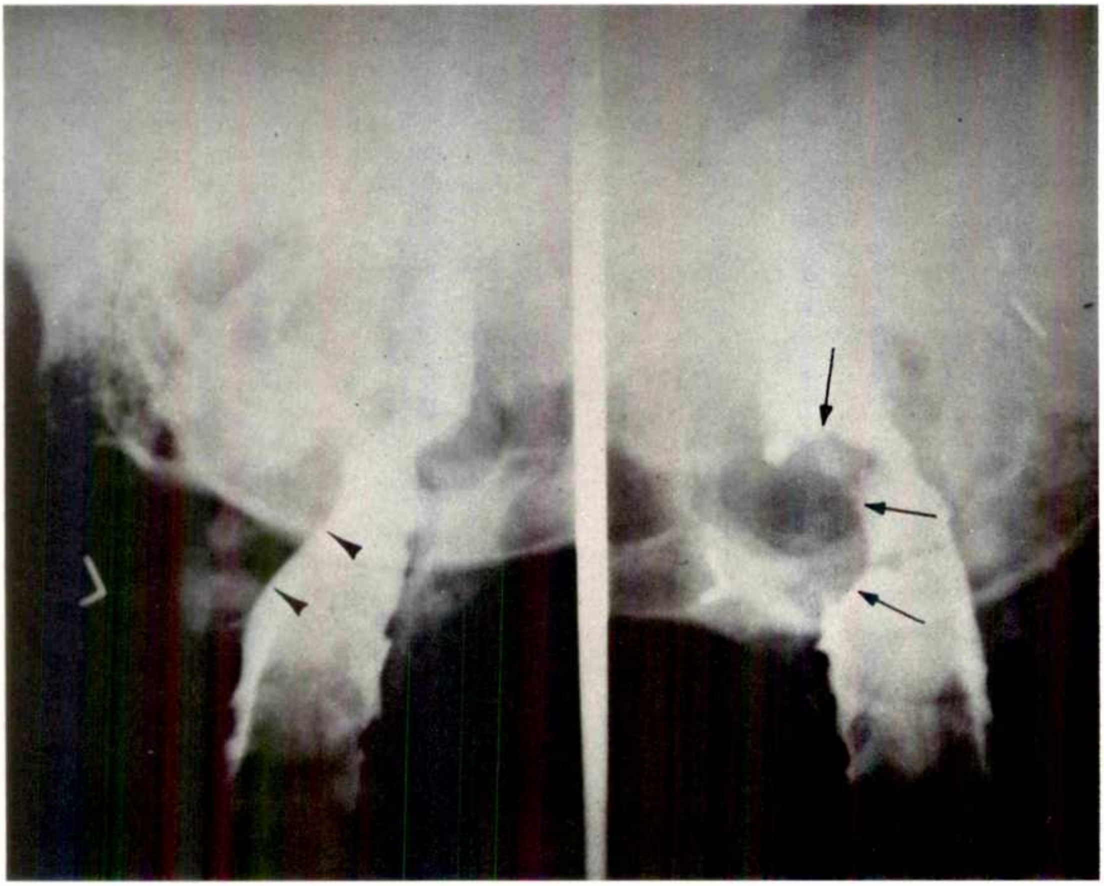


A

(A) Frontal view showing an intradural-extradural mass opposite C_3, C_2 and C_3 on the left side (arrows).

B

(B) Lateral view showing lobulated posterior intradural mass opposite C_1, C_2 and C_3 (arrows). Surgical clips are from a previous biopsy operation.

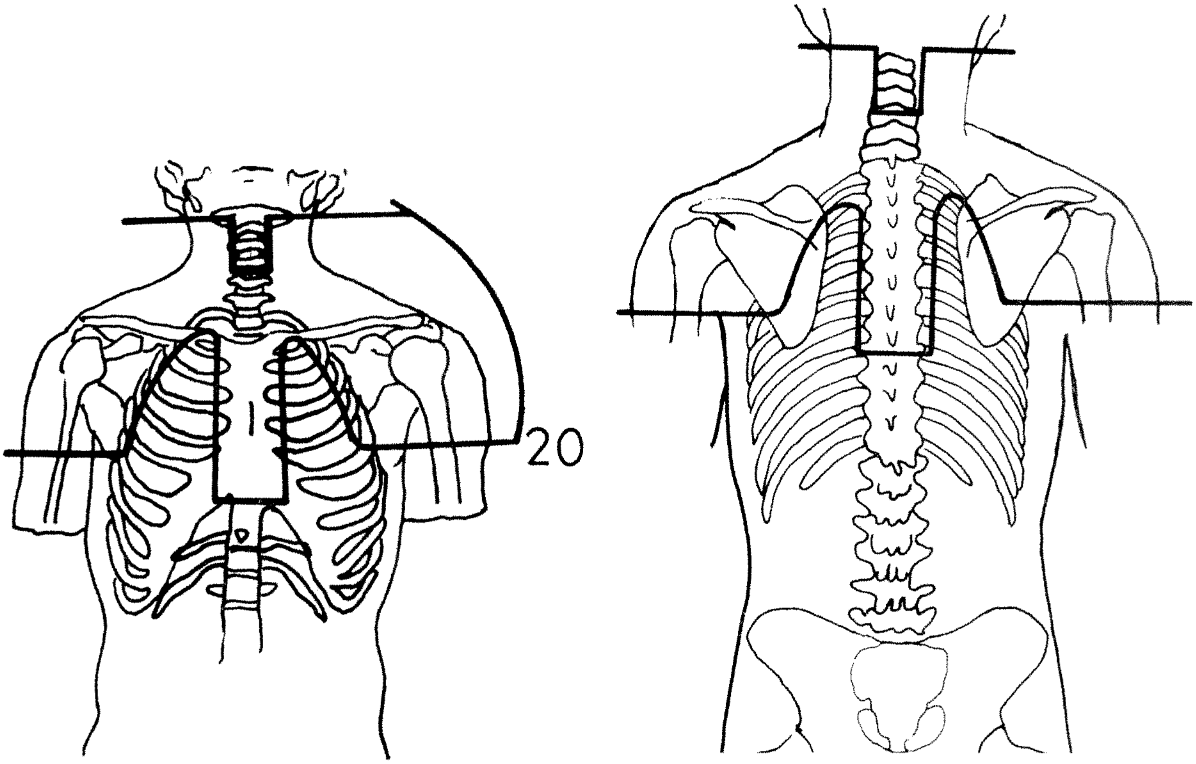


C

FIG. 2.

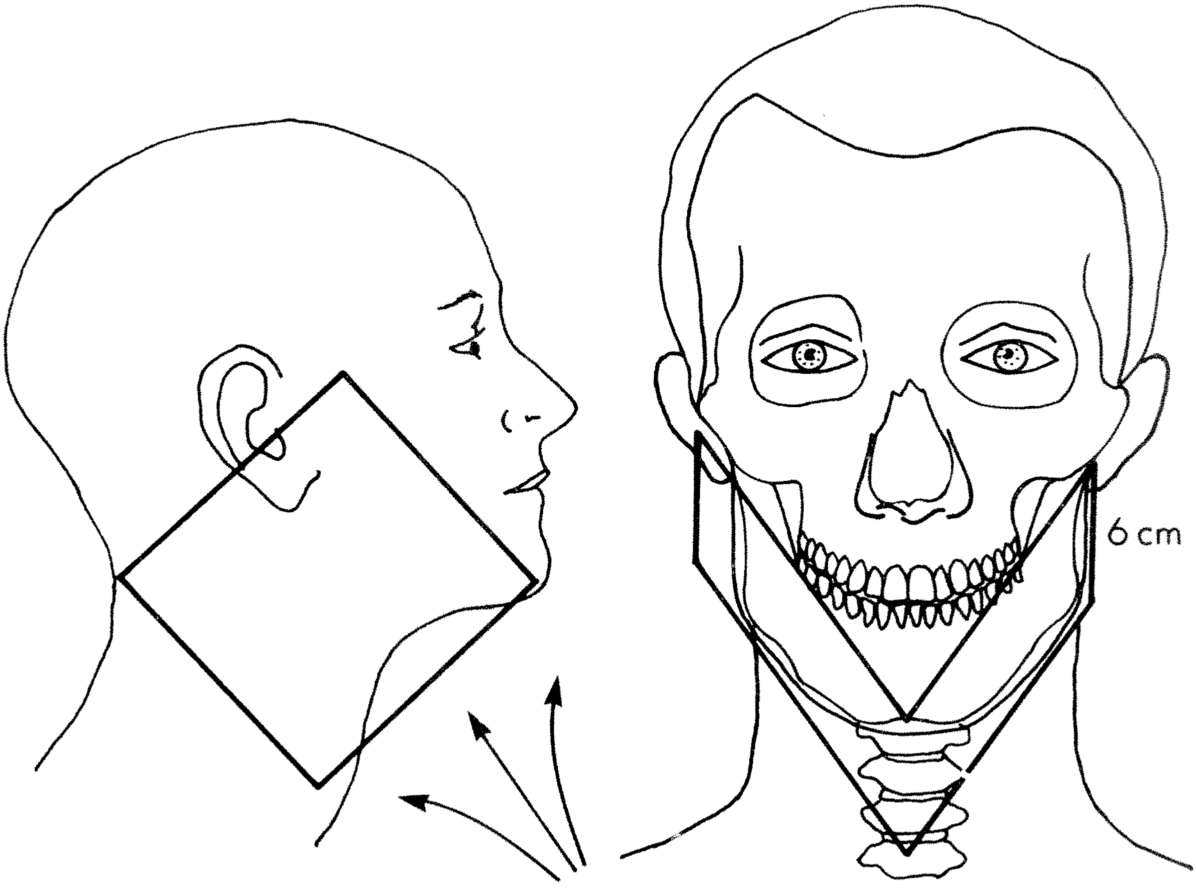
Cervical myelogram.

(C) Oblique views showing: (left) an extradural mass on the left opposite C_1 and C_2 (arrowheads) with medial deviation of the subarachnoid space and the spinal cord; (right) the intradural lobulated portion of the mass (arrows).



A (left) A (right)

Fig. 3 (A) Diagrams of radiation treatment portals for the neck, supraclavicular, axillary and mediastinum lymph nodes (stage II–A Hodgkin's).



B (left) B (right)

Fig. 3 (B) Diagrams of radiation treatment portals for recurrence in the right tonsillar region.

difficult to resect but all the intradural portion was removed. Efforts to remove the extradural portion completely were unsuccessful so the lesion only partly resected. There was one nerve root involved within the mass, and this was removed. No evidence of invasion of the surrounding bone and soft tissue was noted. The cord at the level of the mass was normal. Following surgery, the patient's left sided weakness improved.

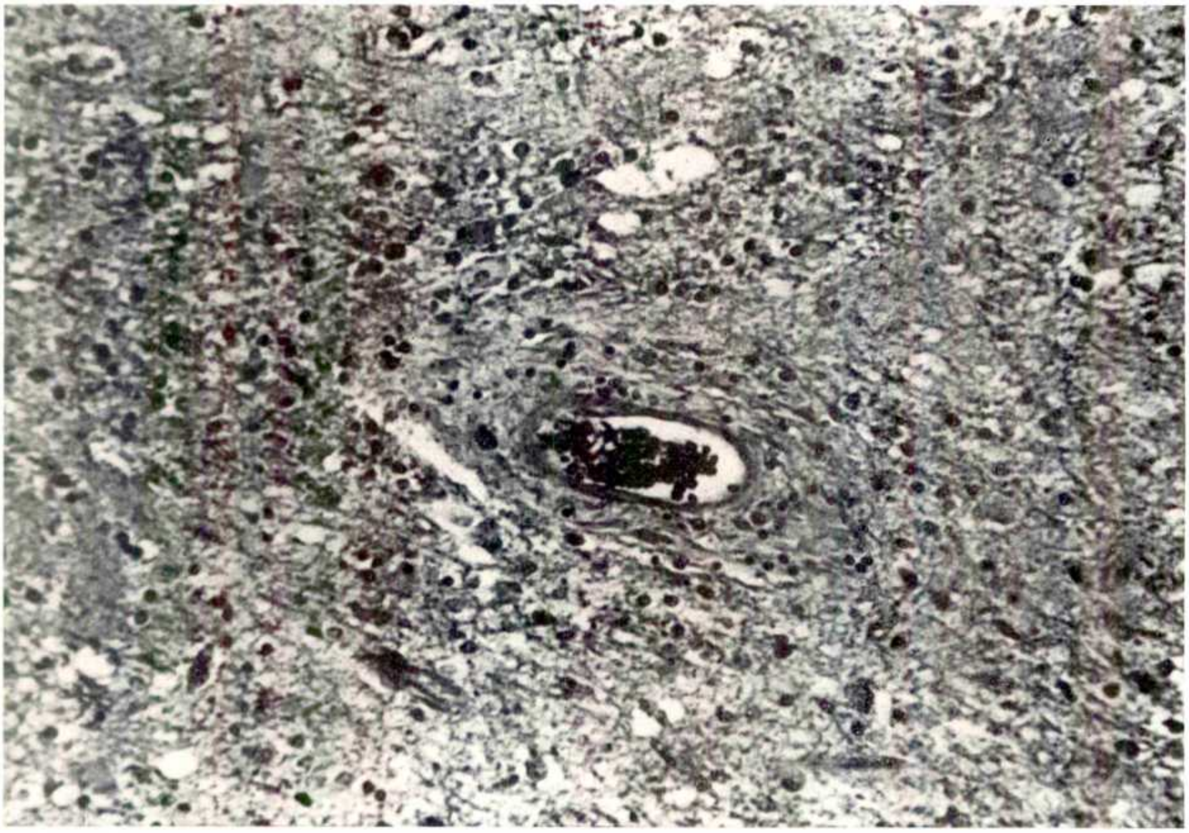
Histopathological examination revealed advanced fibrosis surrounding the nerve root affected, distortions in axis cylinders, demyelination and fibrous replacement of some nerve fibres. Several small arterioles showed thickened, hypercellular media and prominent endothelial cells with vacuolated nuclei which projected into the lumena. Aggregates of mononuclear inflammatory cells were scattered throughout, but were often localized to a perivascular distribution (Fig. 4). The histological slides were reviewed by two different neuropathologists who agreed that the findings were consistent with delayed radiation induced necrosis of a spinal nerve root (ganglioradiculopathy). No evidence of Hodgkin's disease was seen in the entire resected mass (Fig. 4).

Seven months later the patient presented with renewed symptoms and recurrence of the mass. This time the lesion was removed by wide excision and removal was presumed complete. The surgical specimen showed the same histopathological findings. Post-operatively, the patient again improved and has been neurologically stable for the past 15 months.

DISCUSSION

The spinal cord appears to be considerably more sensitive to irradiation and has a smaller margin of safety than the brain (Kramer and Lee, 1974). Experimental work on animals has shown that delayed degeneration of spinal nerves can follow doses of radiation which are near the clinical range. Nerve endings and terminal fibres are more radiovulnerable than the peripheral nerves and roots (Haymaker and Lindgren, 1970). Radiation changes are related to the total dose and probably to the daily fractions. The changes are delayed and less frequent at smaller doses (Stoll and Andrews, 1966; Haymaker and Lindgren, 1970; Janzen and Warren, 1942).

The little that is known of the radiovulnerability of the human peripheral nervous system is based largely on observations of effects on neural elements



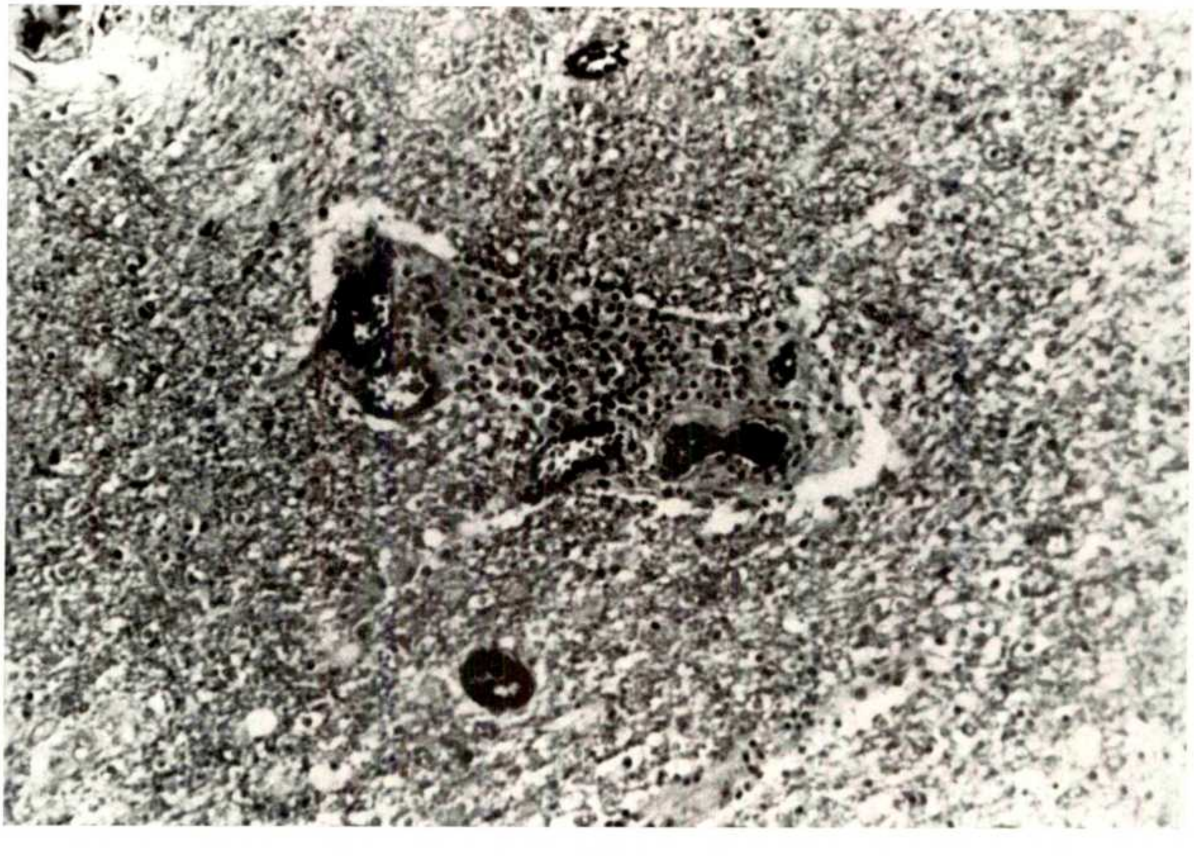
A

Photomicrographs showing characteristic vascular changes of delayed radiation necrosis.
(A) A small vessel showing thickened fibrotic media and adventitia. Notice the fibrous replacement of the normal nervous elements. (PTAH stain ×40).

trans-irradiated in the course of therapy for neoplasms. Tolerance doses are not known. It was shown that neurological symptoms could be elicited in the distribution of the brachial plexus in cases of breast cancer irradiated with doses that ranged from 5775 to 6300 rad given in 11–12 fractions over a period of 25–28 days. It was estimated that in these cases the brachial plexus had received 5100 to 5500 rad. The incidence of neuropathy was 73% with the higher dose (5500 R) and 15% with the lower dose (5100 R) (Stoll and Andrews, 1966; Haymaker and Lindgren, 1970). In other series the estimated minimal dose to the brachial plexus associated with neuropathy was 4100 rad in nine fractions over 18 days with an incidence of 10–20% (Stoll and Andrews, 1966).

It is worth noting that pain, objective sensory disorders and occasionally weakness in the distribution of the brachial plexus have occurred from 5–30 months after radiation with the majority occurring from 10–22 months (Stoll and Andrews, 1966). In another report, these neurological disturbances occurred as late as two to six years post-exposure and in one patient as long as nine years after irradiation of the mammary and axillary regions (1700–2400 R in divided doses). In one study carried out 17 years after repeated exposure of the cervical region and axilla to hard X rays (dose not given), histopathological examinations revealed advanced fibrosis surrounding the nerves and fibrous replacement of some nerve fibres (Hicks, 1953; John, 1946).

In the case presented in this report, the clinical and radiological findings suggested a pre-operative diagnosis of an intradural mass with an extradural extension, in the upper cervical region. On reviewing the dose reconstruction maps of the areas that received radiation, it was clear that the spinal cord was well shielded during the first course and probably received a dose of less than 2000 rad (Fig. 3). When the patient presented with recurrence in the



B

FIG. 4.

(B) Small vessels showing thickened adventitia and perivascular infiltrates of mononuclear cells. Notice the diffuse fibrosis and distortion of the histological pattern. (PTAH stain ×40).

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right tonsillar area eight months later, he was treated with an electron beam (15 MeV) directed submentally. The energy of the electron beam at 15 MeV does not penetrate tissues deeper than 5–6 cm. It was assumed that the vertebral bodies shielded the spinal cord. Thus, it would appear that from both treatment plans the spinal cord itself was shielded but the nerve roots being lateral to the shielded area received a much higher dose. Seven months later the patient presented with regrowth of the partly resected mass. Recurrence of radiation induced masses has also been noted in cases of cerebral radionecrosis (Mikhael, 1978).

The bone was destroyed on the same side at the level of C_2–C_3. Although bone biopsy was not obtained there was no evidence of invasion of the surrounding bone or the soft tissue at the time of surgery. The destruction could have been due to radiation and/or pressure effect.

The author was unable to find any previous reports of delayed radionecrosis of the spinal nerve roots presenting as an intraspinal mass. It is important to recognize this possibility at the time of radiotherapy and to shield the nerve roots whenever possible. Masses of radiation necrosis should be considered in the differential diagnosis of intraspinal masses in the field of previous radiation therapy.

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An unusual cause of thoracic inlet obstruction

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A rare complication of achalasia of the cardia is described which presented as partial asphyxia from tracheal compression at the thoracic inlet.

CASE HISTORY

A 65-year-old woman was referred as an emergency to The Westminster Hospital with a history of increasing difficulty in breathing associated with intermittent swelling of the neck. So dramatic were her symptoms that the referring physician considered her to be in danger of asphyxiating. He also observed that the severity of these attacks was directly proportional to the size of the swelling in the neck.

Her past history centred around a diagnosis of achalasia of the cardia made at the age of 19, which had been managed in the subsequent 46 years by successive mercury balloon bouginage, followed by gastrotomy and manual dilation in 1938 and Heller's cardiomyotomy in 1948 and 1963.

Dysphagia for solids had developed after the last operation and caused her to survive on a diet of liquids and semi-solid food.

Examination revealed a soft symmetrical swelling of the neck which increased markedly in size and tension on coughing or during a Valsalva manoeuvre (Figs. 1 and 2). The thyroid gland and pre-tracheal tissues were normal on examination and no mass was evident on quiet breathing. No other physical abnormality was found.

The plain radiograph of the chest revealed a large right para-mediastinal air-containing viscus which extended from the diaphragm to the level of the aortic knuckle (Fig. 3). Above this a large round "cyst" occupied the right apex (Fig. 4). This was correctly interpreted as representing a grossly dilated but empty oesophagus with a redundant segment lying horizontally at the right apex, which rose into the neck when a Valsalva manoeuvre was performed (Figs. 5 and 6).

Barium swallow revealed that although there was no food debris in the oesophagus, considerable hold-up occurred at the cardia and pooling of contrast medium took place in the upper oesophageal "cystic" component (Fig. 7). Cine radiography showed that with each swallow there was progressive enlargement of the dilated cervical oesophagus

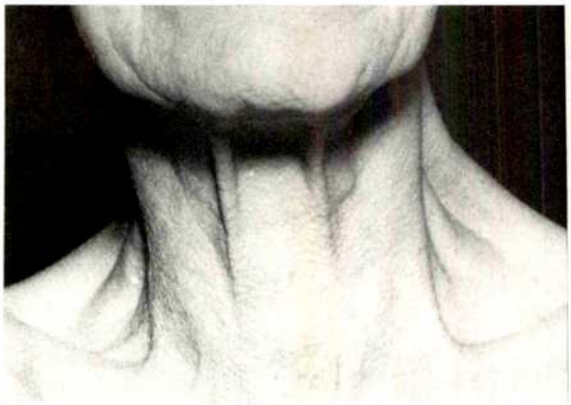

FIG. 1.
Frontal view of neck during quiet respiration.

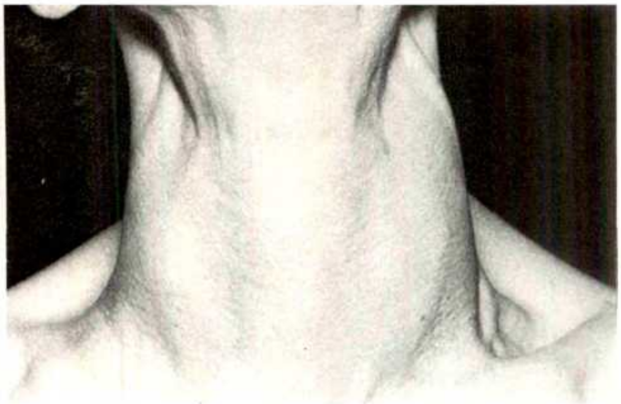

FIG. 2.
During Valsalva manoeuvre the soft tissues "inflate".

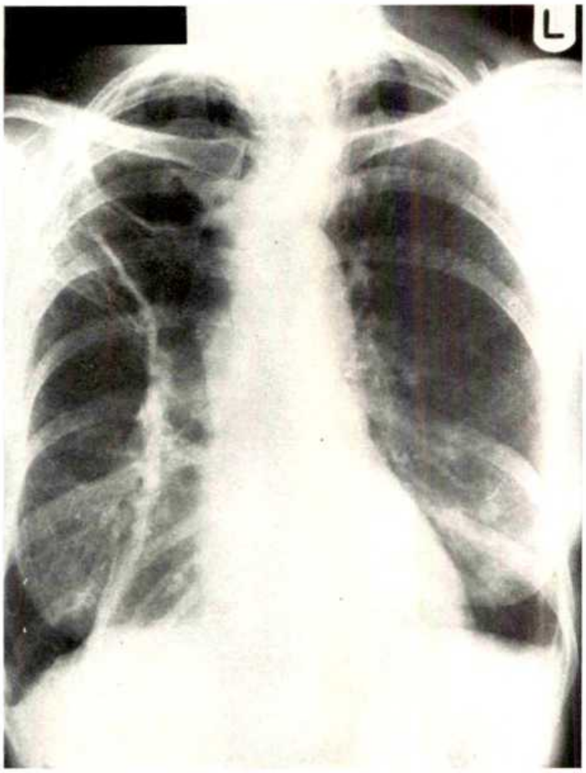

FIG. 3.
PA radiograph on admission showing right para-mediastinal air-containing viscus.

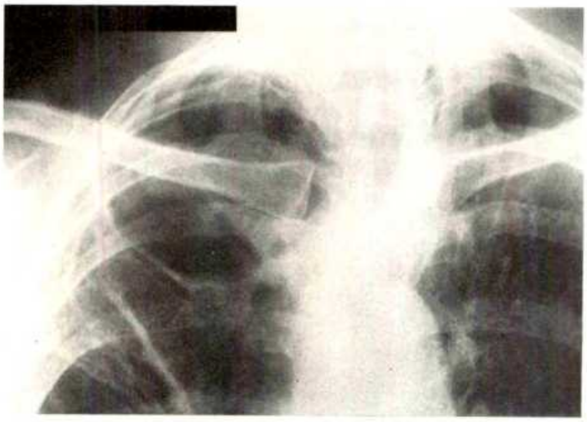

FIG. 4.
Coned radiograph of apical "cyst".

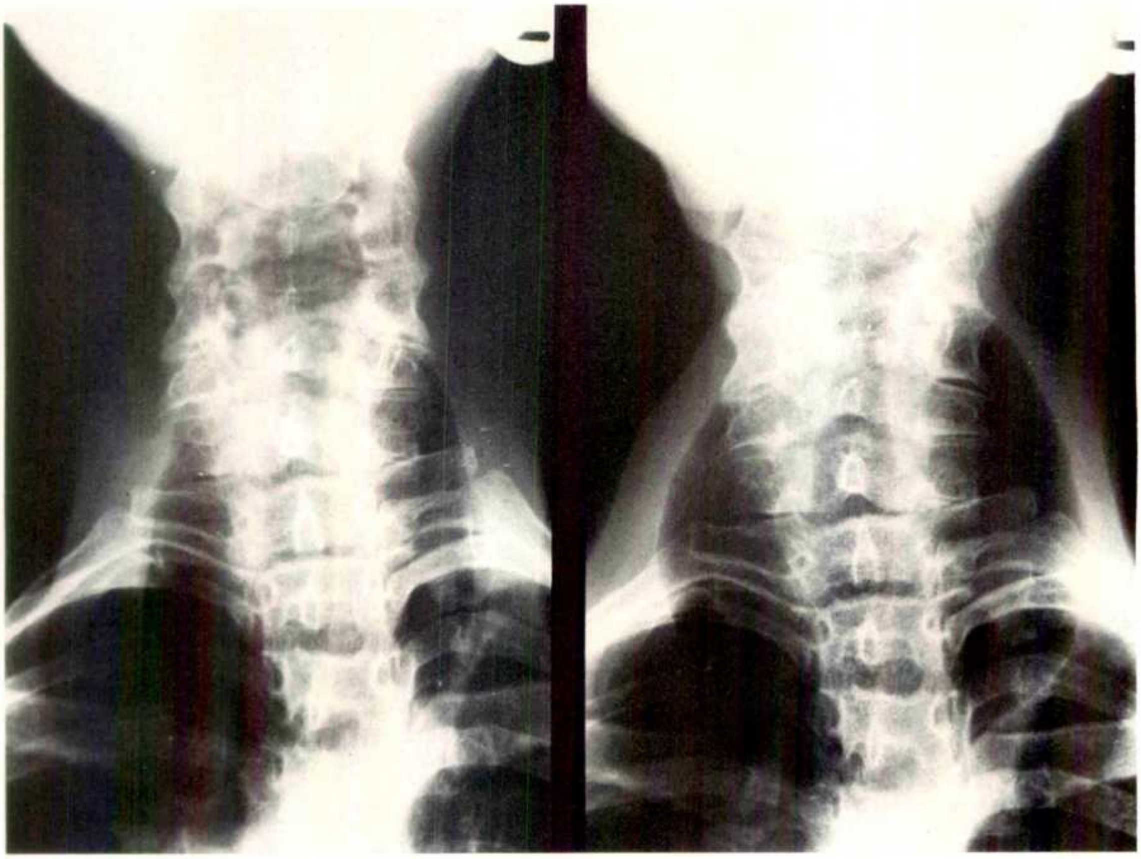

FIG. 5. FIG. 6.

Film of cervical region on quiet breathing and on Valsalva manoeuvre, the air filled viscus balloons above the thoracic inlet (compare with Figs. 1 and 2).

producing compression of the trachea at and above the thoracic inlet.

At operation the whole of the oesophagus was found to be markedly dilated and tortuous. There was especially gross dilation of the upper third of the oesophagus which filled the entire thoracic inlet and which appeared to be constricted inferiorly by the azygos vein indenting the oesophageal lumen. A 15 cm section of oesophagus was resected, the azygos vein was ligated and divided and the cardia was dilated by the passage of a finger. Post operative recovery was good, there being no return of symptoms. Barium swallow three months later shows no evidence of obstruction and no tracheal compression.

DISCUSSION

Achalasia as a cause of thoracic inlet obstruction was first reported in 1950 in a 75-year-old patient who presented with stridor and a "bull neck" appearance (Bello *et al.*, 1950). A similar but more acute swelling of the neck due to achalasia was reported in 1976 in a patient who was in the recovery phase of general anaesthesia (McLean *et al.*, 1976). Tracheal compression alone, apparently without neck swelling has also been recorded (Giustra *et al.*, 1973). In each of these cases, however the condition was previously undiagnosed and untreated.

In contrast, the present patient had received many forms of treatment, apparently with some success and the tracheal compression had resulted from an air distended rather than food distended oesophagus. The mechanism for this air entry into the oesophagus in such abnormal quantities has been postulated by d'Abreu *et al.* (1971) as being due to acquired incompetence of the crico-pharyngeous muscle which allows air to enter the oesophagus on inspiration. We believe that the air thus taken into the oesophagus may be displaced upwards into the cervical region either by increasing the intrathoracic pressure during the Valsalva manoeuvre or coughing or by actual volume displacement during the intake of food. Rather than being expelled, the air within the cervical oesophagus remains trapped

Case reports

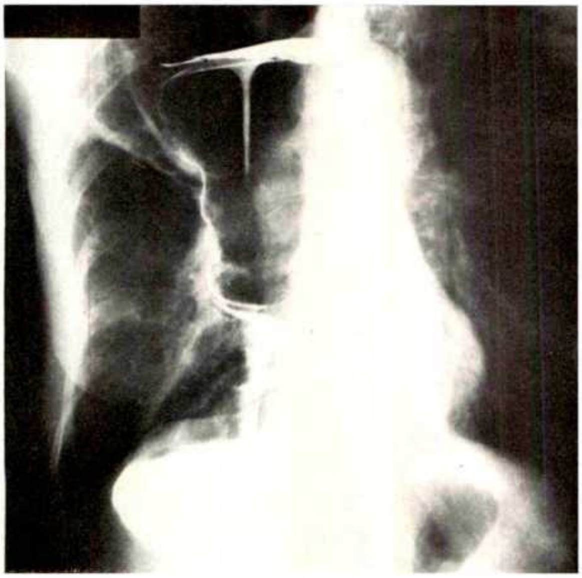

FIG. 7.

Barium outlines the dilated air filled oesophagus. Note the size of the upper part of the oesophagus.

by a pinch-cock valve formed artificially by the dilated, redundant section folding over on itself.

Alternatively it is possible in this particular patient that air in the cervical oesophageal loculus was prevented from being displaced downwards by extrinsic compression from the azygos vein stretched across its lower border.

Whatever the explanation it is apparent that very rarely a chronically dilated oesophagus, distended with air but empty of food, may produce serious symptoms and signs of proximal airways obstruction by compressing the trachea at or above the thoracic inlet.

ACKNOWLEDGMENT

We wish to thank Mr. Charles Drew, F.R.C.S., Senior Thoracic Surgeon to Westminster Hospital, under whose care this patient was admitted, for permission to publish this case.

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Fibroepithelial ureteric polyps

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Benign polyps of the ureter are rare. Most frequently they are composed of fibroepithelial tissue. They may present radiologically as ureteric obstructions, most commonly at the uretero-pelvic junction, or may be seen incidentally as smooth filling defects in the ureter on contrast examination.

CASE REPORTS

Case 1

A 15-year-old white male presented with left abdominal pain and a feeling of pressure in the left flank area. He had no relevant previous history.

On examination the left kidney was palpably enlarged. Urinalysis revealed 1+ protein, 100–150 red blood cells per high powered field and calcium oxalate crystals. The serum creatinine was 0.8% and corrected creatinine clearance was 97 ml per minute.

Intravenous urography suggested left uretero-pelvic junction obstruction. This was confirmed by a frusemide urogram. The ureter distal to the uretero-pelvic junction obstruction was poorly visualized due to low flow of contrast. Neither antegrade nor retrograde pyelography was performed.

At surgery the obstruction was found to be due to five finger-like polyps extending 1.5 cm from the wall of the ureter (Fig. 1). Frozen section revealed these to be benign, and a local resection and pyeloplasty were performed. Histologically the polypoid tumour was composed of large amounts of loose, oedematous fibrovascular stalks harbouring smooth muscle which communicated with the muscle of the ureteric wall. The polyps were covered by normal transitional epithelium.

Case 2

A 22-year-old white female presented with symptoms typical of left renal colic. Previous medical history was negative.

An intravenous urogram demonstrated a calculus in the distal portion of the left ureter causing partial obstruction. Moderate caliectasis was noted on the right and a thin linear polypoid defect in the proximal ureter was seen and confirmed on subsequent follow-up urogram and retrograde pyelogram (Fig. 2).

At surgery a long stalked polyp was locally resected. Histologically this was lined with regular transitional epithelium overlying a fibrovascular stroma containing connective tissue and blood vessels (Fig. 3).

DISCUSSION

The differential diagnosis of uretero-pelvic junction obstruction and radiolucent ureteric filling defects should include benign and malignant neoplasms. Both are rare, especially the benign variety, the most common being the fibroepithelial polyp. These arise from mesodermal tissue and are also known as fibrous polyps, fibromyxomas and myxomas. They are reported with greater frequency than other polyps possibly because of their propensity to become large and mobile enough to cause symptoms.

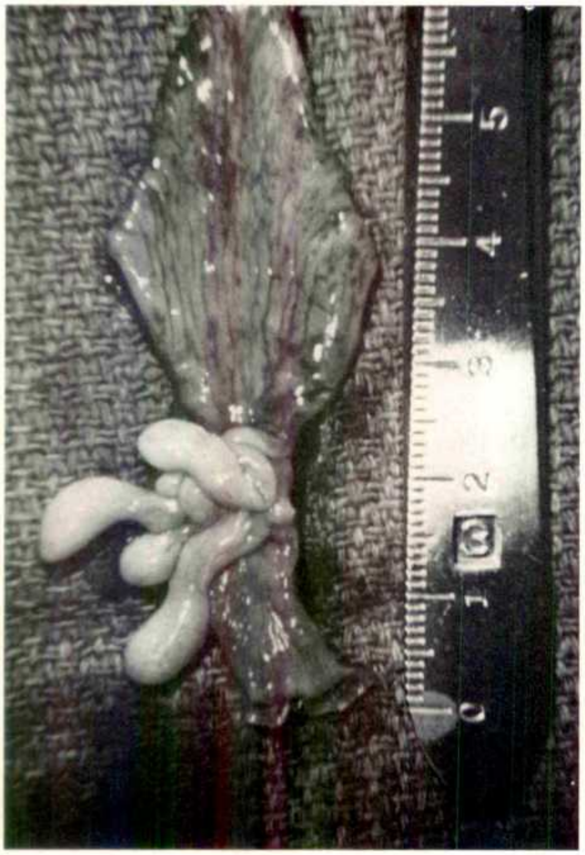

FIG. 1.

Gross specimen of the resected five finger polyp arising from the proximal ureter.

Approximately 50 cases of fibrous polyps were discovered on review of the literature (Banner *et al.*, 1979; Davides and King, 1976; Stuppler and Kandzari, 1975). These polyps can occur in all ages, the youngest patient being four years and the oldest 72 years, with the greatest number in the 20–40 age group (Stuppler and Kandzari, 1975). They are most commonly found in the proximal ureter and frequently cause uretero-pelvic junction obstruction. The most common presenting symptoms are flank pain and haematuria.

The diagnosis can be suggested preoperatively if a well demarcated, pedunculated filling defect is found during intravenous urography. Malignant ureteric tumours are more likely to cause a shorter filling defect with an irregular, shaggy outline, and occur more commonly in older patients. The latter are also more apt to completely obstruct the ureter and cause severe hydronephrosis (Crum *et al.*, 1969).

Local excision and ureteric reconstruction rather than nephroureterectomy has been recommended as the treatment of choice in view of the benignancy of

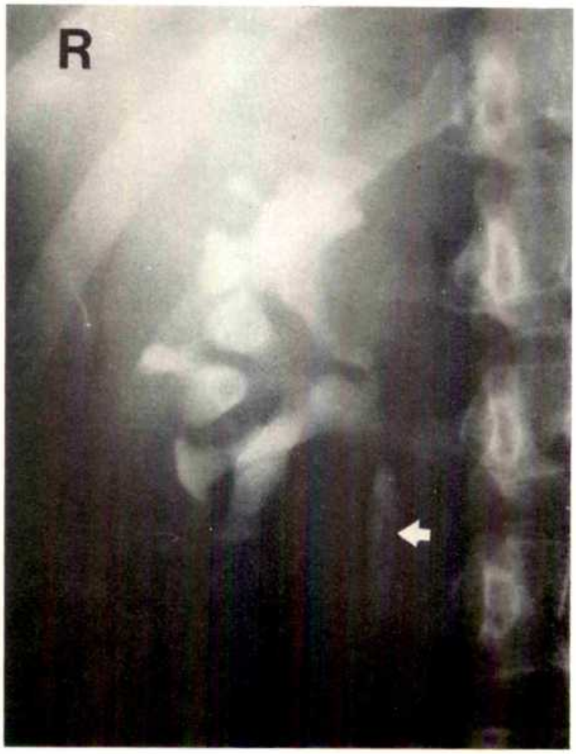

FIG. 2.

Intravenous urogram, right kidney. There is moderate, generalized caliectasis. There is a long polypoid radiolucent defect in the proximal ureter just distal to the uretero-pelvic junction (←).

these polyps. The nature of the lesions can be obtained preoperatively by brush biopsy. If Grade 1 and 2 malignant cells are found, a localized resection can still be performed. If grade 3 or 4, a total nephroureterectomy should be performed. Malignant transformation is uncommon although a 17-year-old has been reported by Davides and King (1976) with a well differentiated transitional cell carcinoma at the tip of a fibrous ureteric polyp.

The aetiology of these polyps is uncertain. Since they often present at an early age they may be congenital, although obstruction, trauma and chronic irritation cannot be entirely excluded (Soderdahl and Schuster, 1969).

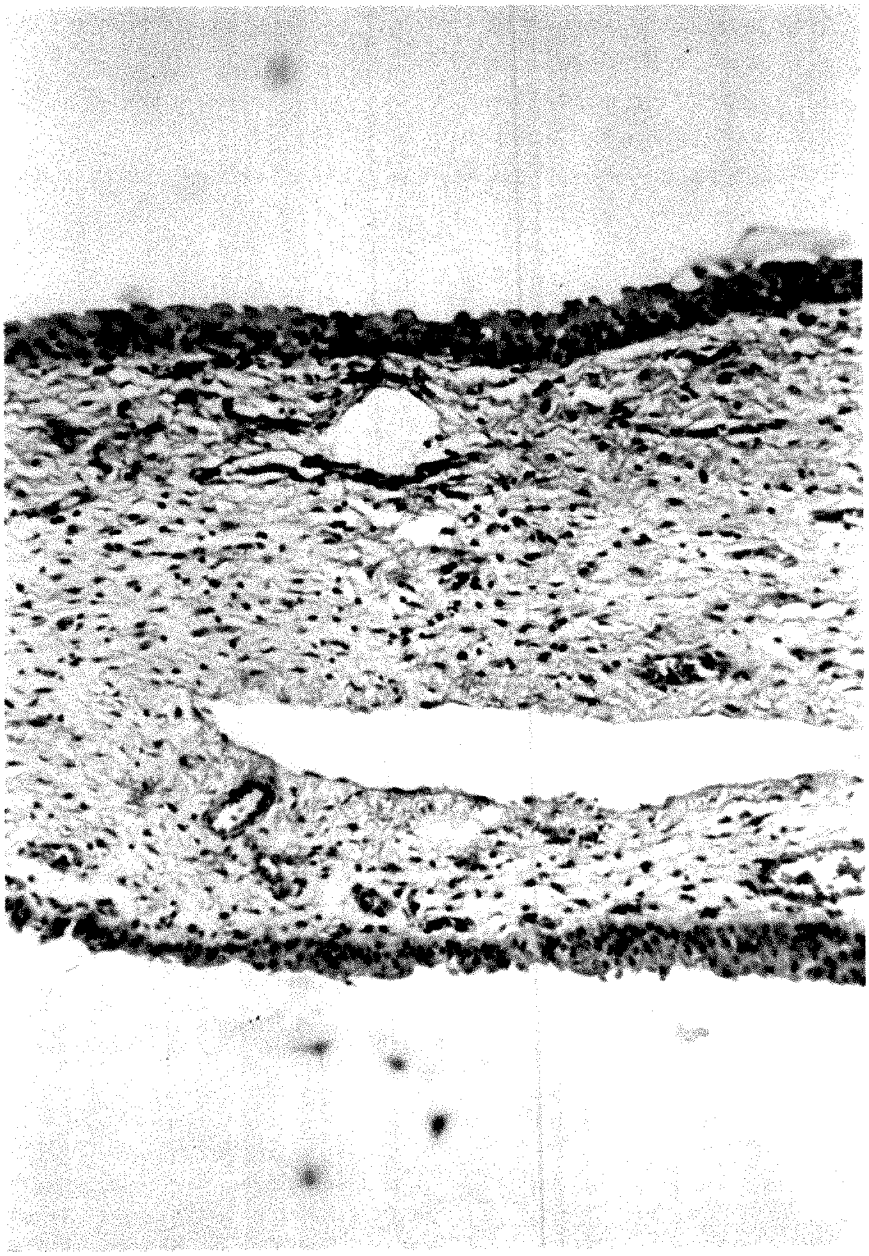

Fig. 3.

Photomicrograph (medium power) of the resected polyp. Normal transitional epithelium covers a stroma containing loose connective tissue and numerous blood vessels.

1979, *British Journal of Radiology*, *52*, 916–917

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Intradural extramedullary aspergilloma complicating chronic lymphatic leukaemia

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Intradural extramedullary masses causing compression of the spinal cord consist almost exclusively of benign tumours, the majority being neurofibromata and meningiomas (Epstein, 1976), while lipomata (Caram *et al.*, 1957), dermoids, epidermoids and teratomas (McCarty *et al.*, 1959) are occasionally encountered. Less commonly compression may be due to malignant tumours, usually metastases from primary brain tumours (Sagerman *et al.*, 1965) or more rarely from sites outside the nervous system.

Spinal cord compression in the lymphomas and leukaemias is usually due to an extradural deposit with or without bony involvement (Verity, 1968; Mullins *et al.*, 1971). Since these lesions are radiosensitive and urgent treatment is often indicated, radiotherapy may be undertaken without histological evidence of the nature of the lesion.

Inflammatory lesions causing cord compression are not uncommon but are almost exclusively extradural and are often associated with adjacent bony involvement (Browder and Myers, 1937). Intradural inflammatory lesions are rare and usually cause arachnoiditis. Since no example of an intradural extramedullary inflammatory mass complicating leukaemia has been reported we would like to document this case because of its therapeutic implications.

Case History

A 52-year-old, married housewife had a five year history of chronic lymphatic leukaemia, treated with corticosteroids (5–10 mg daily) and chlorambucil. During this period she had remained in the chronic phase of the disease with a raised white cell count and hepatosplenomegaly and a slight anaemia. IgA was reduced but IgG was at the lower limits of normal. In May, 1977 she developed transient numbness of the right side of the face with severe ataxia and vertigo suggesting a brain-stem lesion. Cerebro-spinal fluid at that time demonstrated an excess of lymphocytes. She made a gradual but incomplete recovery without treatment.

During the spring and summer of 1978 transient pulmonary infiltrates were noted on chest radiographs, but sputum culture for aspergillosis proved negative at that time. In September, 1978 she was admitted with a two week history of generalized malaise, pyrexia, cough, pain between the scapulae, a progressive thoracic paraparesis and urinary retention. The CSF showed 100 polymorphs and 427 lymphocytes per millilitre. Radiographs of the spine and chest at that time were normal. Myelography was undertaken using metrizamide. There was irregularity of the theca anteriorly, between D7 and D9 with a number of separate intradural extramedullary defects at that level (Fig. 1a). There were also discrete nodules on the surface of the cord throughout its length (Fig. 1b). There was no evidence of bony involvement or para-vertebral soft tissue mass. Computed tomography of the spine undertaken at the same time was unhelpful.

A decompressive thoracic laminectomy was undertaken and the presence of an intradural mass was confirmed on the right side at D7 extending anteriorly, infiltrating and involving the cord and its adjacent roots. In addition, 4 cm proximally there were three circular white deposits attached to nerve roots. There was no extradural component and no sign of meningeal inflammation. Histology demonstrated fungal mycelia consisting predominantly of hyphae with some yeast-like elements, later confirmed as aspergillus fumigatus.

She was treated with amphotericin B intravenously and intrathecally and flucytosine orally, but after some initial improvement her paraplegia became worse. A further myelogram two weeks later demonstrated complete obstruction at D5 while contrast introduced through a cisternal puncture demonstrated obstruction at the lower cervical level. She was given further amphotericin B both intrathecally and intravenously as well as through an Ommaya reservoir, but gradually deteriorated and died approximately one month after admission. Post-mortem examination was refused.

Discussion

Opportunistic infections are becoming more frequent in patients with malignant disease due to deficient immunological competence as a result of drug therapy or irradiation (Young *et al.*, 1970; O'Connell *et al.*, 1973; Ingwer, *et al.*, 1978). In most cases involvement of the central nervous system is part of a systemic dissemination of the fungus and

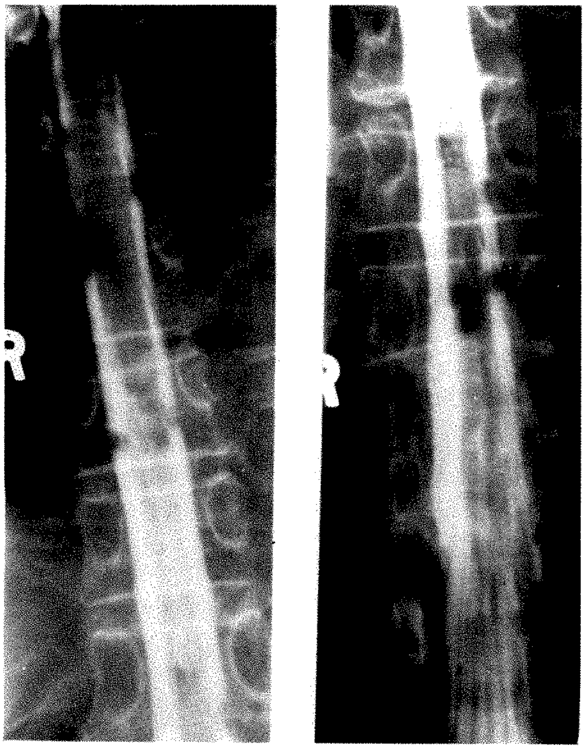

FIG. 1.

Water-soluble contrast myelogram in the mid-dorsal region.
(A) AP view demonstrating multiple intradural extramedullary masses.
(B) AP view of the cauda equina demonstrating small nodules attached to nerve roots.

even then intracranial infection is far more common than involvement of the spinal cord (Mukoyama *et al.*, 1969; Seres, *et al.*, 1972).

Neurological complications involving the spinal cord are uncommon in the lymphomas and even rarer in leukaemia. Diamond *et al.* (1960), in a large series covering 30 years up to 1956, found a 2.7% incidence of spinal cord involvement in 3725 patients with lymphoma, but only 0.7% in 1864 patients with leukaemia. The vast majority of these were extradural masses and no comment was made about intradural deposits. Other authors report an incidence of 3 to 5% of spinal cord involvement in Hodgkin's disease (Thies *et al.*, 1961; Murphy and Bilge, 1964; Newall 1965).

Involvement of the neuraxis by aspergillosis occurs almost exclusively as a terminal manifestation of the disease and few patients survive, ours being no exception. An intradural extramedullary mass in a patient with diminished immunological competence raises the possibility of an opportunistic infection, since such an appearance due to metastatic disease is rare. Intrathecal fungal infection is extremely difficult to diagnose without positive histology since the mycelia are almost invariably undetectable in the cerebro-spinal fluid and the value of other more specific investigation may be limited because of cortico-steroid treatment.

Although these patients frequently require urgent treatment, the demonstration of such a lesion therefore requires histological confirmation before radiotherapy is undertaken.

ACKNOWLEDGMENT

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Case reports

Extrapleural extraosseous costal echinococcosis

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(*Received April 1979*)

Primary hydatid cysts arising in the thoracic wall are apparently extremely rare. Bonakdarpour *et al.* (1973) reported six cases of hydatid disease with rib involvement bringing the total number of cases reported in the western literature under the heading of costal echinococcosis up to 38. His cases included three patients with the extraosseous form of the disease in whom rib erosion was produced by contiguity. Only one of these patients had a primary extrapleural cyst. Similarly in a series of 45 patients with intrathoracic hydatid disease (McPhail and Arora, 1967) there was only one patient with an extrapleural hydatid cyst and he presented with smooth rib erosion thought radiologically to be probably due to tumour.

Case Report

A 41-year-old woman presented with an itching eruption over the extremities and face suspected to represent "chronic" urticaria for which a panel of screening tests and a chest radiograph were requested. She was found to have severe anaemia which proved to be secondary to iron deficiency. Biopsy of the skin lesions showed findings of non-specific dermatitis.

The chest radiograph (Fig. 1) showed a lobulated sharply delineated soft tissue mass on the left side, inseparable from the posterior thoracic wall, associated with marked notching of the inferior aspect of the sixth rib posteriorly and widening of the sixth intercostal space (Figs. 1 and 2). The lesion was initially thought to represent an intercostal neurogenic tumour; however, because of a 10% eosinophilia the serological studies for hydatid were done and were positive. The mass was excized together with the adjoining ribs and it proved to be a single extrapleural hydatid cyst.

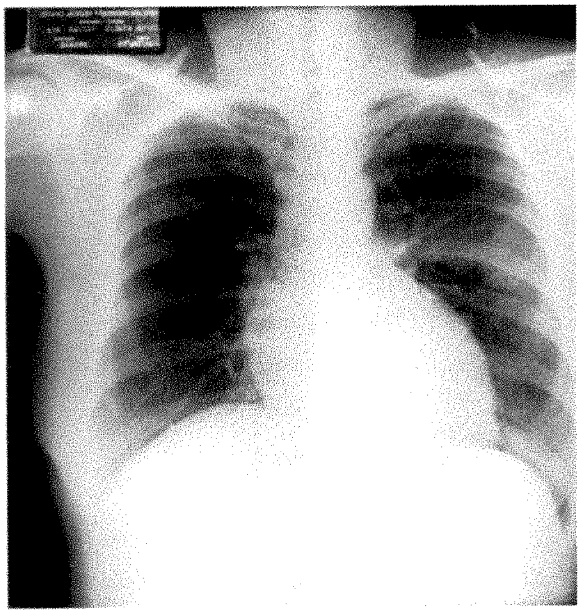

Fig. 1.

PA chest film shows lobulated soft tissue mass causing widening of the left sixth intercostal space and notching of the inferior aspect of the sixth rib.

Discussion

Rib notching associated with an extrapleural soft tissue mass is commonly encountered in patients with intercostal neurogenic tumours such as neurofibroma and neurilemmoma (Boone *et al.*, 1964; Drexler *et al.*, 1964). This case shows an identical appearance produced by an extrapleural extraosseous costal hydatid cyst. Although in the differential diagnosis of rib notching (Wilson, 1960; Boone *et al.*,

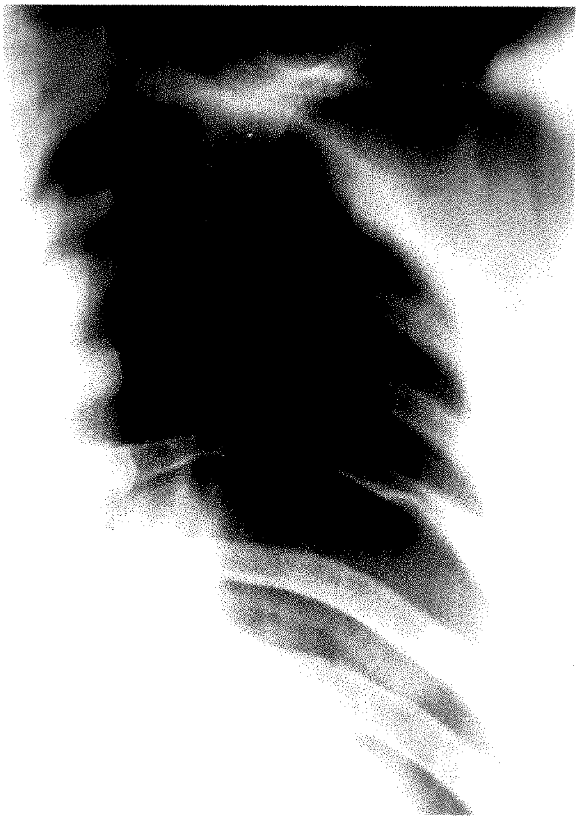

Fig. 2.

Posterior tomographic cut shows the notching of the sixth rib to a better advantage.

1964; Drexler *et al.*, 1964) hydatid disease is usually not mentioned, rib erosion due to long-standing pressure has been reported in peripherally located pulmonary hydatid cysts with pleural extension (Jonathan, 1960; Bonakdarpour *et al.*, 1973). Likewise, rib and vertebral erosion together with separation of neighbouring eroded ribs are known to occur in primary posterior mediastinal echinococcosis (Rakower and Milwidsky, 1960) and in hydatid cysts of the thoracic inlet (Bonakdarpour *et al.*, 1973). In these locations, hydatid cysts may simulate neurogenic tumours (Rakower and Milwidsky, 1960) and "Pancoast tumours" (Bonakdarpour *et al.*, 1973) respectively. In endemic areas, hydatid disease should therefore be considered in the evaluation of lesions associated with rib and/or vertebral erosion.

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Book review

Handbook of radioactivity measurements procedures, NCRP Report No. 58, pp. xiv+506, 1978 (NCRP Publications, Washington D.C.), $11.00.
ISBN 0-913392-41-3

This excellent report, which is an updated version of the first part of the 1961 Manual of Radioactivity Procedures originally issued by the National Bureau of Standards in the USA as Handbook 80, deals mainly with radioactivity standardization procedures. It emanates from a committee chaired by Wilfrid Mann who has spent almost the whole of his working life in the radioactivity standards field at NBS. From both the theoretical and practical aspects this is a most useful publication for anyone undertaking the accurate measurement of samples of radioactive materials. It deals with its subject matter in great detail. It will rarely be of value to the clinician or biologist but it will be a "must" for many physicists and will often replace a well thumbed version of Handbook 80. The preface to the report makes it clear that NCRP (National Council on Radiation Protection and Measurements) intend to issue a further report dealing with measurements of radioactivity for clinical and biological purposes.

Following basic descriptions of radioactivity, the interaction of radiation with matter and terminology of the standardization, the physics of radiation detectors is considered in detail with special attention given to dead-time and other corrections. The core of the book comprises chapters dealing with the theoretical and practical aspects of both direct (absolute) and indirect (comparative) methods for the measurement of radioactivity. Techniques are described for the preparation of standard solutions, and of samples for counting or calibration. A chapter is devoted to the assay and identification of radioactive materials. This includes sections on environmental and low-level radioactivity measurements and on the assay of radiopharmaceuticals. There is an exceptionally clear chapter on the statistics relevant to the measurement of radioactivity. The book itself ends with a short chapter on accuracy and precision in the national and international measurement of radioactivity standards, which refers to the current endeavour to ensure "traceability" to the national laboratories and to NBS in particular.

The handbook includes an appendix consisting of a table of nuclear data for more than 200 radionuclides, prepared from data available to July 1978. The half-life, type of decay, energy and intensity of the emitted radiations are listed together with values of mean energy emitted per nuclear decay. There is a good index and over 600 references are quoted.

The becquerel and gray are referred to in the preface and occasionally in the text but have not yet been wholly adopted

G. R. NEWBERY

1979, *British Journal of Radiology*, *52*, 920–921

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

Solid food label for measurement of gastric emptying

THE EDITOR—SIR,

Measurement of the rate of gastric emptying of solid food by external counting techniques necessitates the use of a radioactive label which is uniformly distributed through the solid, remains attached to the solid in the stomach and is not absorbed.

The main objection to simple methods of labelling solids by techniques which rely on the surface absorption of isotopes (*e.g.* Griffith *et al.*, 1966) has been raised by Meyer *et al.* (1976) who showed that the label may readily dissociate from the solid. For this reason they developed a complicated procedure which requires the *in vivo* labelling of a chicken's liver with $^{99}Tc^m$-sulphur colloid, the subsequent killing of the chicken and the removal and cooking of its liver. In this way the $^{99}Tc^m$ is incorporated uniformly and intracellularly throughout the liver. Their *in vitro* studies showed that less than 10% of the $^{99}Tc^m$ was liberated from the liver.

Another reliable method of manufacturing a solid-food label was employed by Heading *et al.* (1976). They used small pieces of filter paper impregnated with $^{99}Tc^m$-sulphur colloid and then coated with Perspex as a solid-phase marker.

We were required to label a specific carbohydrate-rich breakfast for gastric emptying studies and neither of these methods was suitable. We therefore employed a simple procedure in which $^{99}Tc^m$-tin colloid was incorporated into porridge as a solid-food label. We mixed 3.7 MBq (100 μCi) of $^{99}Tc^m$-tin colloid (Amersham Code No. N112) with warm water and used it to prepare a standard portion of instant porridge. The meal consisted of the porridge with skimmed milk, crispbread with margarine and marmalade, and a glass of orange juice.

Studies *in vitro* showed that the activity remained associated mainly with the solid component of the meal. Samples of the porridge were mixed with various volumes of 0.1 N HCl or gastric juice and gently agitated occasionally for one hour. The preparations were then centrifuged and the activities in the solid and liquid phases measured. The results showed that between 82 and 97% of the activity was associated with the solid phase.

Meyer *et al.* (1976) found that more than 90% of the activity remained associated with their labelled chicken liver, while Heading *et al.* (1976) found that more than 97% of the activity remained attached to the pieces of filter paper. Our results, while poorer than these two methods, are considerably better than the surface absorption method of Griffith *et al.* (1966) who labelled scrambled eggs with ^{51}Cr. *In vitro* measurements of this label by Meyer *et al.* (1976) indicated that up to 90% of the ^{51}Cr became detached from the solid.

During the gastric emptying measurements, which lasted 90 minutes after the end of the meal, blood samples were taken from the subjects at frequent intervals. The maximum value for each study of the percentage of the administered dose per litre of plasma ranged from 0.002 to 0.094. These extremely low plasma levels confirm that the $^{99}Tc^m$-tin colloid was not absorbed and also indicate that there was no breakdown of the $^{99}Tc^m$-tin colloid to produce free $^{99}Tc^m$.

In conclusion, this method provides a simple, reliable method of labelling solid food for gastric emptying measurements which compares reasonably well with more complicated procedures.

Yours etc.,
M. L. FITZPATRICK,
A. M. ALDERSON.

Department of Medical Physics,
Hammersmith Hospital,
London W12 0HS.

(*Received February 1979; revised June 1979*)

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Care with radiosensitizers

THE EDITOR—SIR,

Hendry and Sutton (1978) express concern about the possible sensitizing effect of misonidazole in normal tissues in patients treated with this drug combined with radiotherapy. Their argument is based upon the enhanced effect seen in human normal tissues following treatment in hyperbaric oxygen and upon observations in animals when radiotherapy is combined with hyperbaric oxygen and with misonidazole.

It has been pointed out (Adams, 1978) that there is an essential difference between hyperbaric oxygen and chemical sensitizers with regard to effects upon normally well-vascularized tissue in which the oxygen concentration is fairly high. Following administration of hyperbaric oxygen (3 atmospheres) the concentration of oxygen in venous blood will rise from about 60–70 μM to about 750 μM, most of which will be free and unbound and this will occur in the cells throughout a well-vascularized normal tissue. Although the curve relating the oxygen enhancement ratio (OER) to oxygen concentration tends to flatten out above the 60–70 μM level, there is still a small but significant increase in OER before the maximum value is reached. This increase is equivalent to an additional increment of dose of about 5–10%. This is in accord with clinical observations (Dische, 1978). With misonidazole, however, at the maximum safe doses, the sensitizing effect upon oxic normal tissue cells will be equivalent to that produced by an elevation of oxygen concentration of only about 10 μM—an elevation causing negligible effect in well oxygenated tissues.

With chemical sensitizing agents, as with hyperbaric oxygen, there is, however, a risk of an increased effect in those normal tissues where significant numbers of hypoxic cells are present. The cartilage of the larynx is one site where there is evidence that the concentration of hypoxic cells may be of clinical significance.

The data cited by Hendry and Sutton (1978) certainly indicate that hypoxic cells may occur in some normal tissues in rodents and indeed show that very high concentrations of misonidazole sensitize these tissues to large single doses of radiation. However, it is misleading to infer from results obtained with doses of misonidazole of 1 mg/g that sensitization of normal tissues will occur in man when the doses administered are usually at least 20 times lower. Further, in the experiments quoted by Hendry and Sutton (1978), the single doses of radiation used were very large and usually in the range of several kilorad. Such doses cause extensive killing of oxic cells so that effects upon very small concentrations of hypoxic cells may become critical. To our knowledge no significant misonidazole-induced sensitization of normal tissues has so far been reported in radiobiological studies with multiple fractions.

In our experience at Mount Vernon Hospital with the 180 patients who have been treated with a combination of misonidazole and radiotherapy, the immediate reactions which we have so far observed in all normal tissues have been exactly those to be expected for the radiation dose and fractionation employed. It is too early to make observations concerning late effects. The larynx has been included in the treatment field in 10 cases—no enhancement of immediate reaction has been seen nor has any unusual effect been observed, so far, in limited follow-up.

We agree that we must proceed with caution and recognize a potential hazard with any sensitizing agent. However, for misonidazole in the dosage presently used in a fractionated course of radiotherapy, we believe that the chance of any appreciable increase in normal tissue effect even in the larynx is extremely small.

Yours, etc.,

G. E. ADAMS,

Physics Division,
Institute of Cancer Research,
Sutton, Surrey SM2 5PX.

S. DISCHE.

Marie Curie Research Wing for Oncology,
Regional Radiotherapy Centre,
Mount Vernon Hospital,
Northwood, Middlesex HA6 2RN.

(*Received April 1979*)

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(In reply)

Care with radiosensitizers

THE EDITOR—SIR,

Adams and Dische (1979) comment that the conclusion in our cautionary note (Hendry and Sutton, 1978) drawn from observations in mice, concerning possible radiosensitization of normal human tissues by misonidazole, is doubtful because of (1) relative tolerable drug doses, (2) single versus fractionated treatments, and (3) existing clinical experience.

1. It is unlikely that peak blood plasma levels of misonidazole higher than about 100 μg/ml will be achieved consistently in fractionated human treatments owing to toxicity (Dische *et al.*, 1977). Such levels are achieved in mouse blood plasma by doses of 0.1 mg/g body weight (McNally *et al.*, 1978). Although experiments using normal tissues and 0.1 mg/g have not been reported, radiosensitization of normal rodent tissues has been observed at 0.2 mg/g. It has been pointed out to us by the authors that the latter dose was used in their experiments on mouse skin (Yuhas *et al.*, 1977), quoted in our letter, where sensitizations by 0%, 13% and 19% were observed for three types of damage. Also, sensitization by 28% has been reported recently for paralysis following irradiation of rat spinal cord with 0.2 mg/g of drug (Yuhas, 1979). Sensitization at this drug dose is expected only for cells at oxygen tensions much lower than that of venous blood, as demonstrated *in vitro* (McNally and de Ronde, 1978). Such hypoxic cells have, for example, been demonstrated in growing cartilage (Dixon, 1967) and in skin (Field and Bewley, 1974) of mice.

2. The sensitization values above, together with those included previously (Hendry and Sutton, 1978) using higher drug doses (commonly 1 mg/g), were found using large single radiation doses. Similar measurements using multifractionated radiation doses are not available, and this is currently under investigation. It could be predicted that similar sensitization may occur with fractionated doses, since growing cartilage is affected by hyperbaric oxygen (HBO) equally at all radiation doses (Dixon, 1967). Also, some cell populations in mouse skin show marked hypoxia which is dose-modifying, for example, epidermal clones (Withers, 1967), melanocytes in hair follicles (Potten and Howard, 1969), and the target cells for tail necrosis (Hendry, 1978). Reoxygenation during fractionation would diminish the effects of such initial hypoxia, but few measurements of this have been made. For tail necrosis, reoxygenation was observed in "clamping" experiments one week after large single priming doses (Hendry, 1978), but it was not observed with 10 or 15 daily dose fractions (Hendry, unpublished). Using HBO, it was found that mouse skin was sensitized by 39% for single radiation doses, and by 36% using ten daily fractions (Suit and Howard, 1967).

3. Our warning is more relevant for future generations of less toxic or more efficient sensitizers than for misonidazole, with which higher "effective" plasma levels might be achieved. Also, although radiosensitization of early damage in normal human tissues may not be apparent, tissues responsible for late effects may respond differently if these include slightly-hypoxic tissue elements such as cartilage and nervous tissue, where the potential for sensitization exists.

Yours, etc.,

J. H. HENDRY,
M. L. SUTTON.

Paterson Laboratories and Department of Radiotherapy,
Christie Hospital and Holt Radium Institute,
Manchester M20 9BX.

(*Received May 1979*)

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Whole gut perfusion for barium enema preparation

The Editor—Sir,

We were interested to read the paper by King *et al.* (1979) in a recent edition of your Journal. We introduced this method two years ago in King's Lynn, but whereas King *et al.* used the method on unselected cases, we used it on patients who had already had a failed barium enema preparation or who were known to be exceptionally constipated.

Our technique was essentially the same as that described except that we perfused the Hartmann's solution at three litres per hour instead of four.

We abandoned the technique after five cases because of complications in two patients. One, a 34-year-old female, had no result after six litres had been perfused in two hours. She developed polyuria and urinary retention and had to be catheterized. The other problem occurred in a 54-year-old woman, who after five and a half litres had no bowel motion but developed abdominal distension. This gradually disappeared over the next few days following cessation of the perfusion.

Assessment of haemoglobin, blood electrolytes and serum proteins before and after perfusion showed no significant change in any of the five patients.

King *et al.* reported no complications in their 40 cases. Our different experience presumably reflects the fact that we selected exceptionally constipated patients. On the basis of our limited experience we feel that the technique is potentially hazardous in such patients.

Yours, etc.,
J. Stabler,
M. J. Brindle.

West Norfolk and King's Lynn General Hospital,
London Road,
King's Lynn,
Norfolk PE30 5QD.

(*Received June 1979*)

REFERENCE

King, D. M., Downes, M. O. and Heddle, R. M., 1979. An alternative method of bowel preparation for barium enemas. *British Journal of Radiology*, *52*, 388–389.

Book reviews

Bone Dysplasias of Infancy. A Radiological Atlas. By B. J. Cremin and P. Beighton, pp. xiii+109, 1978 (Springer-Verlag, Berlin, Heidelberg, New York), £21·06/DM78.00/ $39.00.
ISBN 3-540-08816-4

Skeletal dysplasias presenting in the neonatal period are uncommon and may thus present considerable diagnostic difficulty to both paediatrician and radiologist. In this short but well produced atlas, Professors Cremin and Beighton, whose contribution to the field of skeletal dysplasias is well known to readers of this Journal, have produced a helpful aid to diagnosis.

The atlas restricts itself to those conditions identifiable at birth and in the main does not attempt to show serial changes in the dysplasias—indeed, such an approach is already available. After short but helpful chapters on genetics and antenatal radiography, each disease is presented with its salient clinical and radiographic manifesttations. The descriptions are very brief, but excellent comments are provided on each condition. The references, in particular, are very comprehensive. The illustrations are, as always from this publisher, excellent and include, as should be mandatory in any radiological text on dysplasias, clinical photographs of the affected infants. Differential diagnoses could perhaps have been discussed more fully, but this book is easily read and the appropriate disease should be easily identified.

This atlas does not aim to be comprehensive and succeeds within this limitation. Unfortunately, its price is relatively high for a volume of around 100 pages and other texts currently available probably represent better value for money. None the less, this easily used short atlas will be of help in any department where dysplasias in neonatal life are likely to be encountered.

P. Renton.

Pediatric Orthopedic Radiology. By M. B. Ozonoff, pp. xii +516, 1979 (Saunders, Philadelphia), £22·50.
ISBN 0-7216-7034-2

This is volume 15 in the series of "Monographs in Clinical Radiology", which already includes such valuable books on paediatric radiological subjects as Edward Singleton's *Radiology of the Alimentary Tract in Infants and Children* and Andrew Poznanski's *The Hand in Radiologic Diagnosis*. Dr. Ozonoff's book is likely to prove equally important and can be recommended as an addition to the departmental library.

Most text books of paediatric radiology spend considerable space on nutritional, metabolic and neoplastic bone diseases and the generalized dysplasias. Here these subjects are largely ignored and there is instead a concentration on what are really the more important, everyday diseases of orthopaedic practice. The author has a refreshingly common sense approach. His explanations of the principles of various surgical procedures will remedy a common defect in the knowledge of the radiologist, so allowing him to appreciate the type of information that helps the surgeon in his choice of treatment and in the evaluation of its results. In turn, the orthopaedic surgeon will learn much about the many variations of normal development and radiographic projection effects.

The illustrations are excellent, the text very readable and there is commendable reference to the need to restrict radiation dosage. One sentence on page 33 is worth remembering to quote to the over-enthusiastic: "...... even under the best circumstances the addition of a mere three lumbosacral radiographs exposes the ovaries to a radiation dose equivalent to that given by a daily chest radiograph for six years".

R. Astley.

Forthcoming events

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of the penultimate month preceeding publication (*i.e.* April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Joint Committee on Radiopharmaceuticals

The Joint Committee on Radiopharmaceuticals of the European Nuclear Medicine Society and the Society of Nuclear Medicine would like to hear from laboratories who would be interested in participating in a study to establish a standard procedure for the evaluation of radioactivity on thin layer chromatograms, which would be used for the quality control of radiopharmaceuticals.

On the basis of this collaborative study, a recommendation will be made to the European Pharmacopoea Commission for inclusion in the Pharmacopoea.

Interested laboratories should contact: Dr. P. H. Cox, Co-ordinating Chairman, Joint Committee on Radiopharmaceuticals, c/o the Department of Nuclear Medicine, Rotterdamsch Radio Therapeutisch Instituut, Rotterdam.

Nuclear Medicine Versus The Rest

To be held on November 14, 1979, this meeting is to review the present contribution of nuclear medicine to the investigations and diagnosis of disease in the context of competing techniques. It is hoped to define the limitations of particular applications and indicate areas for potential growth. There will be three sessions including review papers covering applications in: 1. lungs and cardiovascular system; 2. GI tract and urinary system and 3. skeletal and other systems.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

Radiobiology Meetings

The three work-in-progress meetings this year 1979/80 will be "The role of the stroma in radiation responses" on November 16, 1979, a general meeting on February 15, 1980 and "Biological effects of doses below 2 Gray" on May 16, 1980. Also, there will be an all day-meeting, with invited speakers on Satudray, December 8, 1979, "The rationale for unorthodox fractionation". All meetings will be held in the Institute's Reid-Knox Hall.

Information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

The British Medical Ultrasound Society 11th Annual Scientific Meeting

To be held on December 17–18, 1979 in Edinburgh.

Address for enquiries: Dr. W. N. McDicken, Department of Medical Physics and Medical Engineering, The Royal Infirmary, Edinburgh EH3 9YW.

Modern Gastrointestinal Radiologic Techniques for the Practising Physician

San Francisco, January 26–27, 1980.

For further information contact: Radiology Postgraduate Education Section Room M396, University of California, San Francisco, California 94143 or call (415) 666–5731.

Radiology in the 1980s

A seminar critically appraising the use of imaging techniques will be held in the Clinical Research Centre, Harrow, on February 28–29, 1980. Early registration is recommended as the number of participants will be limited. Details from Dr. G. de Lacey, Northwick Park Hospital, Watford Road, Harrow, Middx. HA1 3VT.

Whither Neuroradiology?

An evening meeting to be held on January 18, 1980, organized jointly with the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and the Royal College of Radiologists. Speakers will include Prof. T. Sherwood, Drs. I. F. Moseley, B. S. Worthington, I. G. Wylie and K. J. Zilkha.

Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

Cell and Protein Labelling with Gamma Emitting Radionuclides for *In Vivo* Studies

A meeting to be held on February 13, 1980 organized by the Nuclear Medicine Committee of The British Institute of Radiology, at Middlesex Hospital Medical School, London.

Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

Investigative Laparotomy in Hodgkins Disease

A joint meeting of The British Institute of Radiology, the Royal Society of Medicine (Section of Radiology) and the Royal College of Radiologists to be held on February 15, 1980, organized by and held at the Royal Society of Medicine, London.

Third Annual Refresher Course

The Society of Computed Body Tomography will offer its Third Annual Refresher Course, March 2–6, 1980 at the Del Coronado Hotel, San Diego, California. The course will include an assessment of "state of the art", 2–5 second CT body scanners, dynamic CT scanning, new insights into thoracic and abdominal anatomy as seen with CT, and CT-guides interventional techniques. The relationship of CT to other imaging methods, including ultrasound, nuclear medicine and angiography will be emphasized. The faculty will include Drs. Alfidi, deWinter, Doppman, Evens, Glenn, Goldberg, Haaga, Harrel, Hattery, Kazam, Korobkin, Kreel, Sagel, Sample, Schellinger, Sheedy, Stanley, Stephens and Wittenberg. The fee is $250.

For further information write to Robert J. Stanley, M.D., Mallinckrodt Institute of Radiology, 510 South Kingshighway, St. Louis, MO 63110, USA.

5th International Congress of the International Radiation Protection Association

Will take place in Jerusalem, Israel, March 9–14, 1980.

The scientific programme of the Congress will cover all aspects of radiation protection with emphasis on its central theme: radiation protection—a systematic approach to safety.

An interesting programme has been planned including a commercial exhibition and pre- or post-congress workshops and professional tours.

Social events and a programme for accompanying persons have been organized.

For further information: The Secretariat, 5th International Congress of IRPA., PO Box 16271, Tel Aviv, Israel.

B.I.R. ANNUAL CONGRESS 1980 AND SCIENTIFIC EXHIBITION

The British Institute of Radiology Annual Congress will be held on April 17–18, 1980 at the Royal Free Hospital and will include the Sylvanus Thomson Memorial Lecture, presented by Sir Richard Doll.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

PHYSICAL ASPECTS OF FAST NEUTRON THERAPY

A meeting to be held on April 21–24, 1980 at the Royal Postgraduate Medical School, Hammersmith Hospital, London.

Course fee: £100 including catering. Closing date for applications: February 1, 1980.

Application forms may be obtained from: The School Office (SSC), Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS (01–743 2030 ext. 351).

SYMPOSIUM ON SPINE AND ITS CONTENTS

EAR "Symposium Vertebrologicum" (Spine and its Contents) will be held from April 23–25, 1980, in Prague, Czechoslovakia.

The subjects of this symposium will be recent advances and experiences in:

(a) Equipments and investigative methods of spine and spinal cord.
(b) Radioanatomy and physiology of spine and spinal cord.
(c) Radiodiagnosis of pathological conditions.
(d) Interventive (diapeutic) radiodiagnostic methods.

For further information contact The secretariat of "Vertebro 1980", PO Box 88, Sokolská 31, 120 26 Praha 2, Czechoslovakia.

EUROPEAN SYMPOSIUM ON LUNG CANCER (EAR)

The symposium, organized by the Greek Radiological Society under the auspices of the European Association of Radiology will be held September 7–13, 1980 at Chalkidiki, Greece.

For further information contact the Secretariate, Department of Radiology, Areteion Hospital, 76 Vass. Sofias, Athens, Greece.

MEASUREMENT STANDARDS IN RESPECT OF BOTH IONIZING AND NON-IONIZING RADIATION HAZARDS

An all day meeting with the National Physical Laboratory and The British Institute of Radiology is to be held on May 14, 1980 at the NPL, Teddington, Middlesex.

XV INTERNATIONAL CONGRESS OF RADIOLOGY

The XV International Congress of Radiology will take place June 24–July 1, 1981 in Brussels, Belgium.

The scientific activities of the Congress as well as the scientific and technical exhibitions will take place in the Brussels Exhibition Centre.

Further information from: Secretariat ICR-81, Ave. Winston Churchill 234B-Box 16, B-1180 Brussels, Belgium.

TENTH L. H. GRAY CONFERENCE

Will be held in Oxford on July 13–16, 1981 on "biological actions of radiofrequency, microwave and ultrasonic radiations".

A conference to review and discuss past and current research on the radiobiology and biophysics of the radiations, particularly in relation to their potential therapeutic value.

Information/Chairman of Organizing Committee: Dr. C. R. Hill, Institute of Cancer Research, Royal Mardsen Hospital, Sutton, Surrey.

Obituary

Dr. William L. Caldwell

(November 12, 1929 – May 21, 1979)

We record with regret the accidental death of Dr. W. L. Caldwell at the age of 49. At the time of his death he was associate director of the Wisconsin Clinical Cancer Center. He will be familiar to many British readers for the time he spent at the Royal Marsden Hospital and Institute for Cancer Research in 1963–1964.

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Handbook of radioactivity measurements procedures, NCRP report no. 58 919

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INSTITUTE OF UROLOGY
(University of London)
in association with St. Peter's Hospitals
URO-RADIOLOGY WEEKEND
7th and 8th December 1979
in the Lecture Theatre, Institute of Urology.
Films for quiz will be displayed Friday lunchtime

Topics to include:

Friday, 7th December 1979 2.00 p.m.–6.00 p.m.

The use of C.T. Target Scanning in uroradiological problems	Professor P. F. Van Waes
C.T. of Bladder tumour	Dr. M. J. Kellett
Pulmonary complications of renal failure	Dr. C. M. Parks
Radiology of renal osteodystrophy	Dr. P. Renton

Uro-radiology Quiz

Saturday, 8th December 1979 9.00 a.m.–4.00 p.m. Symposium on Interventional Uro-Radiology

Medical and surgical approach to renovascular hypertension	Dr. F. D. Thompson
Percutaneous Transluminal Angioplasty	
– Technique with peripheral vascular disease	Professor C. B. Puijlaert
– Use in renal artery stenosis–Videotape presentation	
– Discussion	
Cytology of urological and retroperitoneal malignancies	Dr. W. Hyman
Fluoroscopic needle aspiration biopsy	Dr. M. J. Kellett
Ultrasound guided aspiration techniques	Dr. D. Schonfeld
C.T. guided aspiration biopsy	Dr. Janet Husband
– Discussion	
Percutaneous Needle nephrostomy	Dr. H. Saxton
Venous sampling in locating abdominal endocrine tumours	Dr. D. Alison
Embolisation of renal tumours	Dr. T. A. S. Buist
– Discussion	

Fee: £30

Applications to The Secretary, Institute of Urology,
172 Shaftesbury Avenue, London WC2H 8JE
Tel: 01–836 5361, from whom detailed programmes may be obtained

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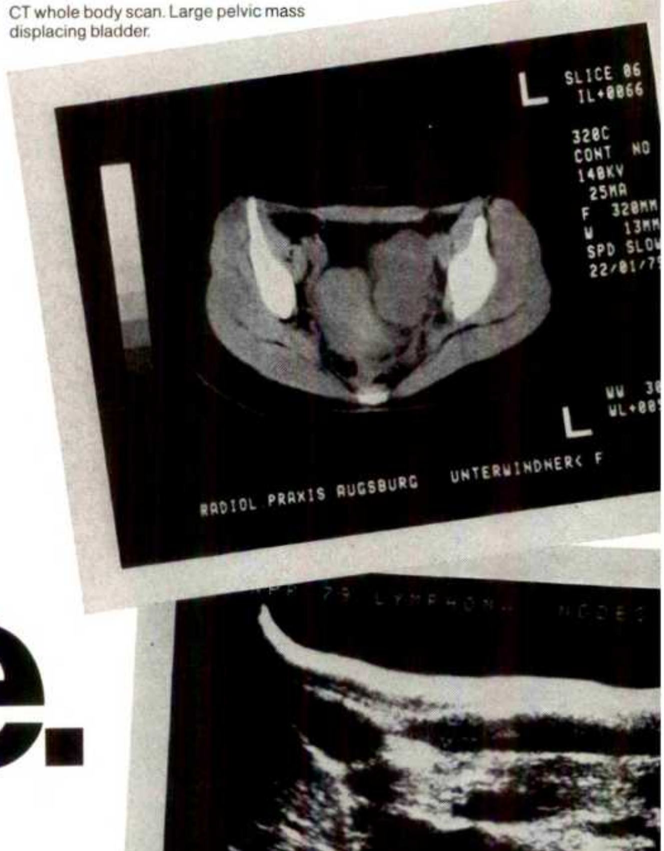

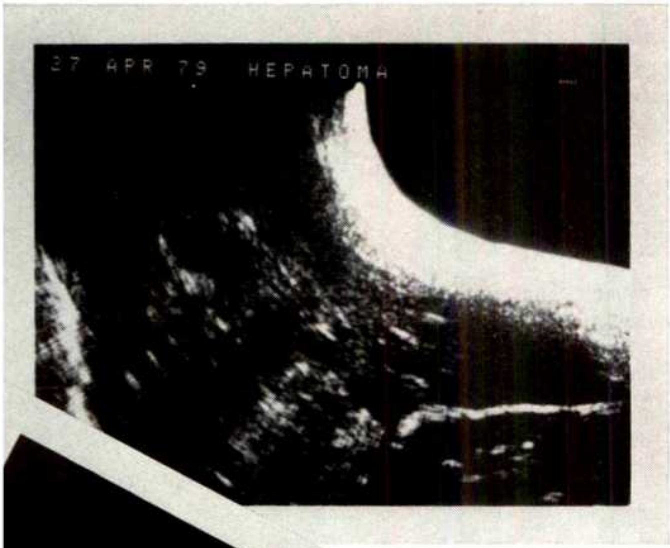

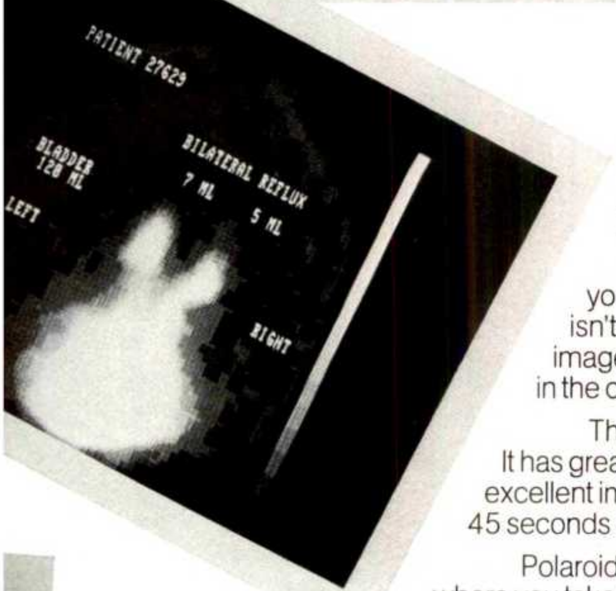

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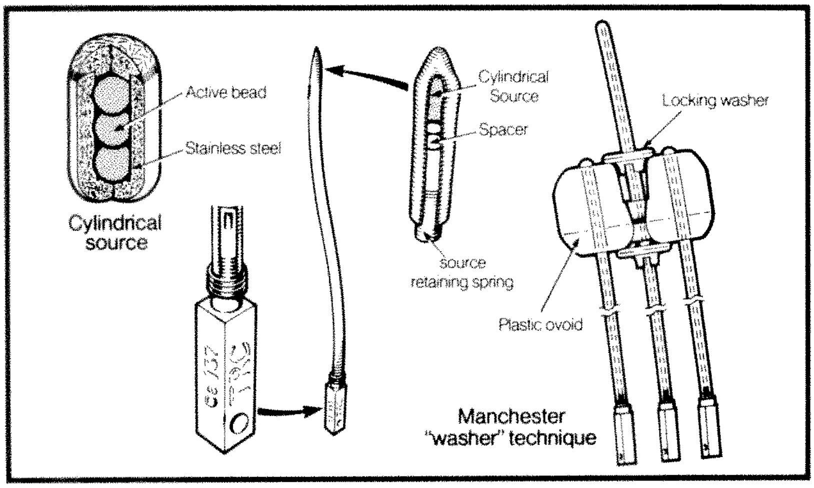

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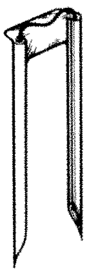

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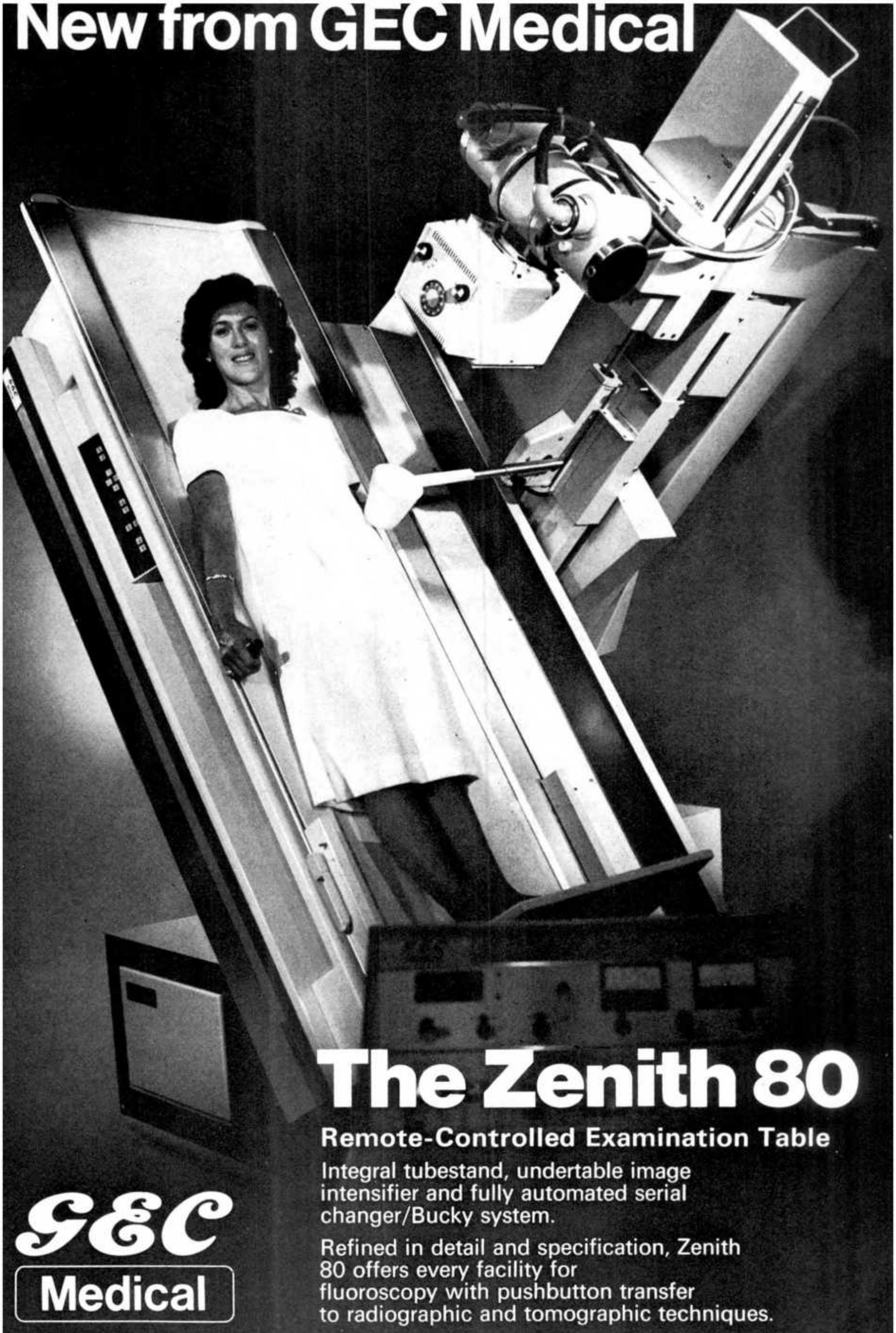

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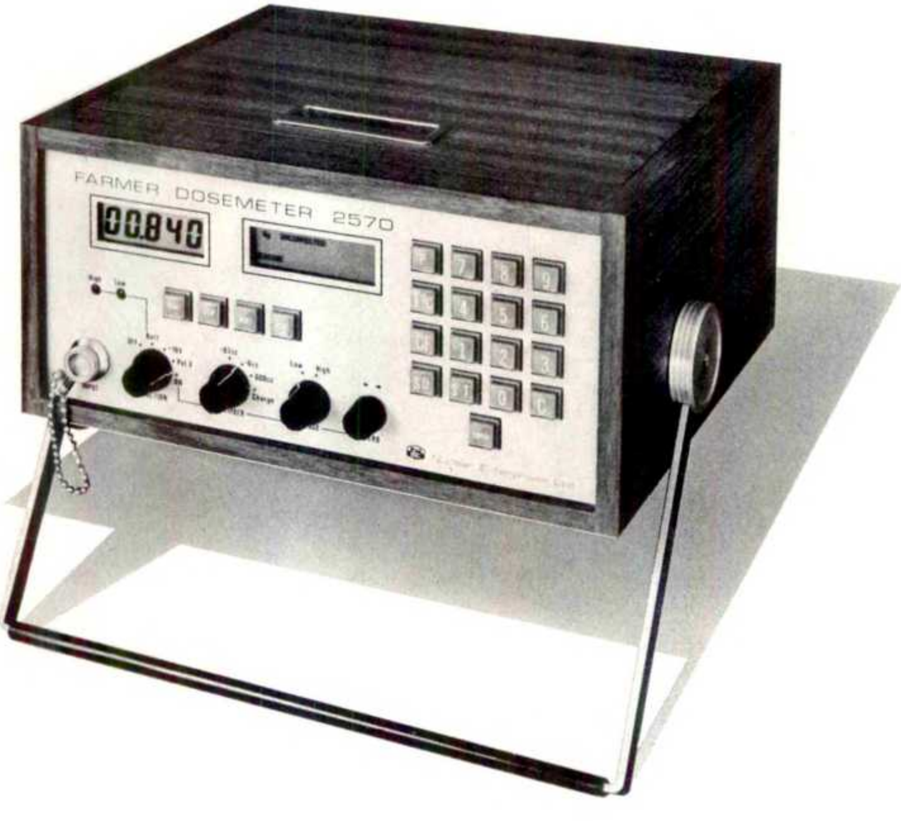

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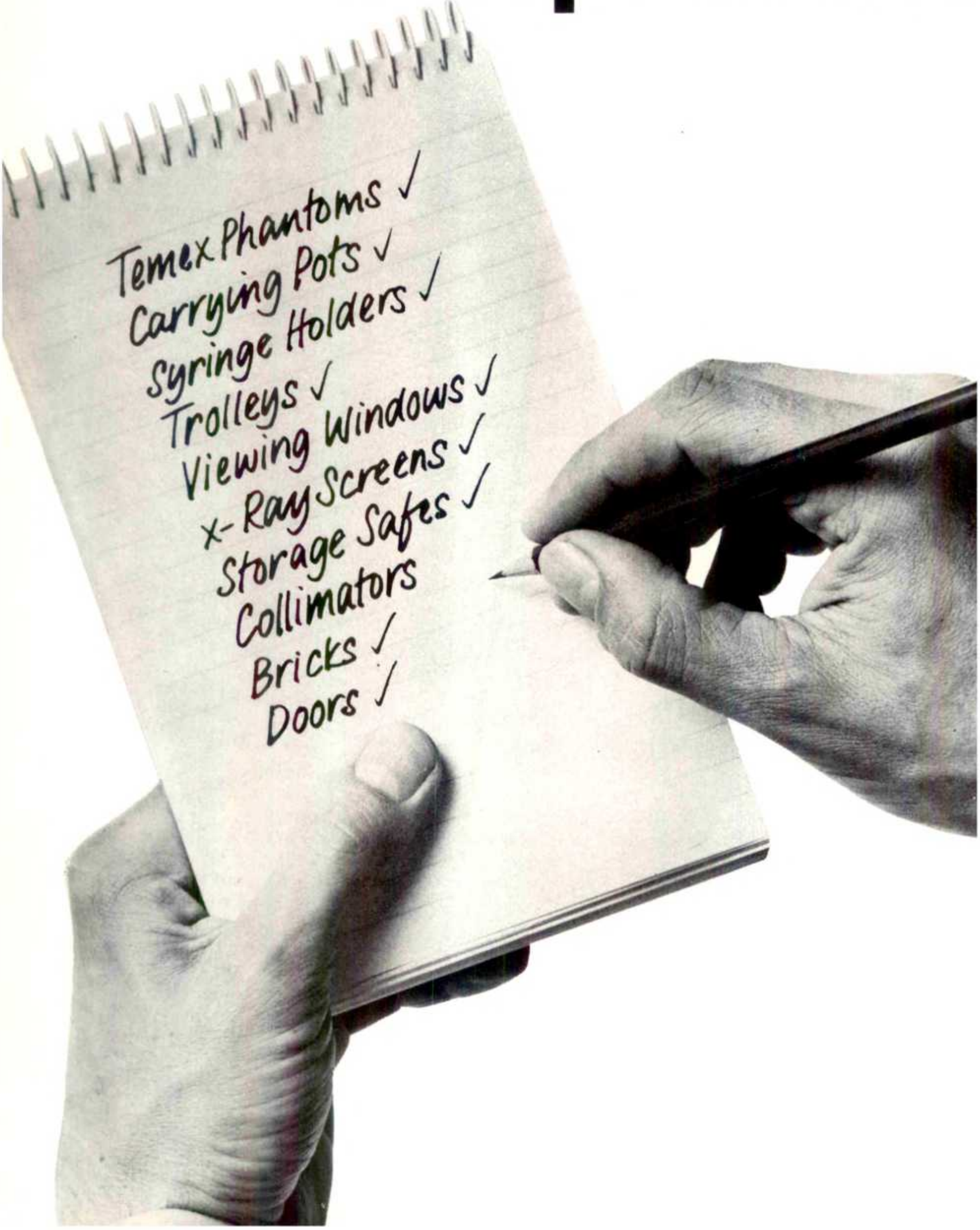

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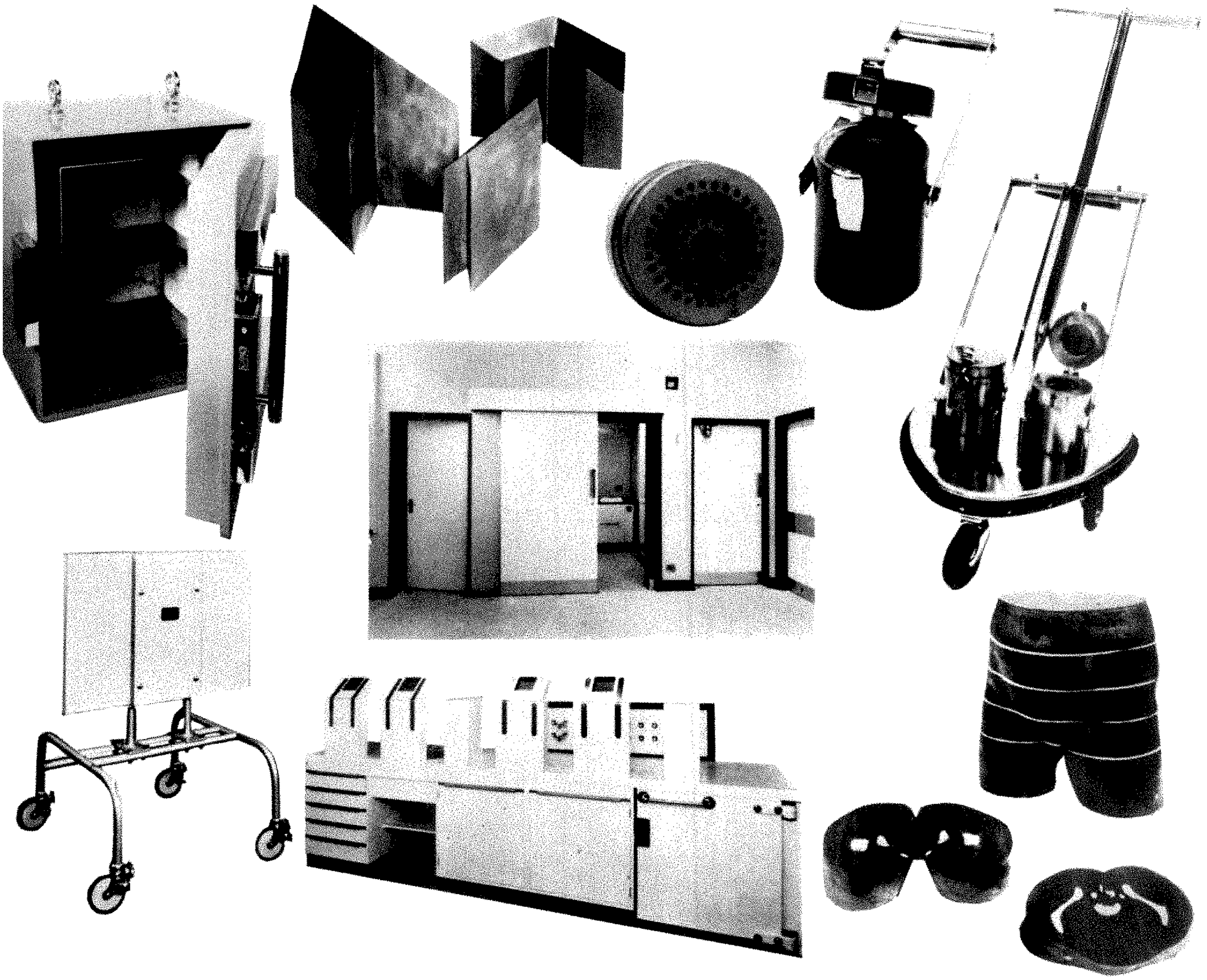

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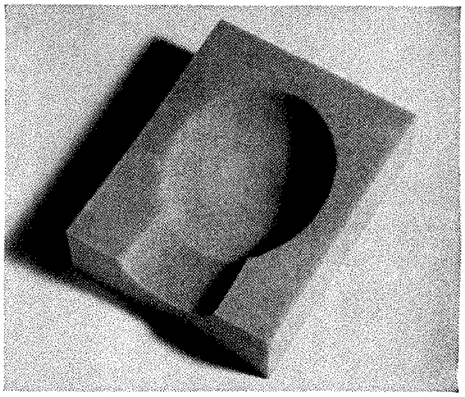

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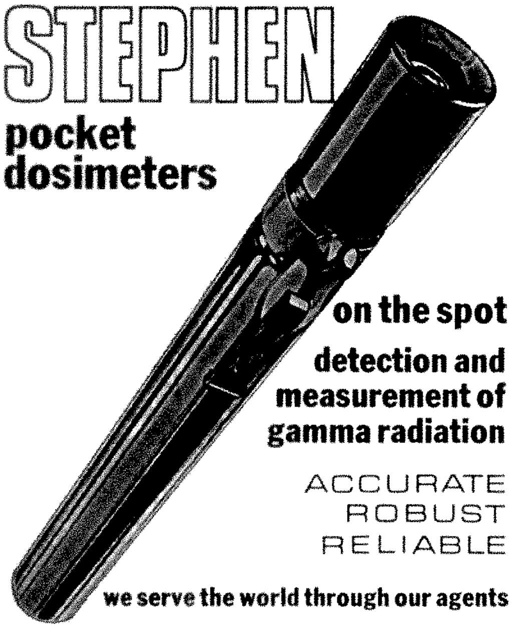

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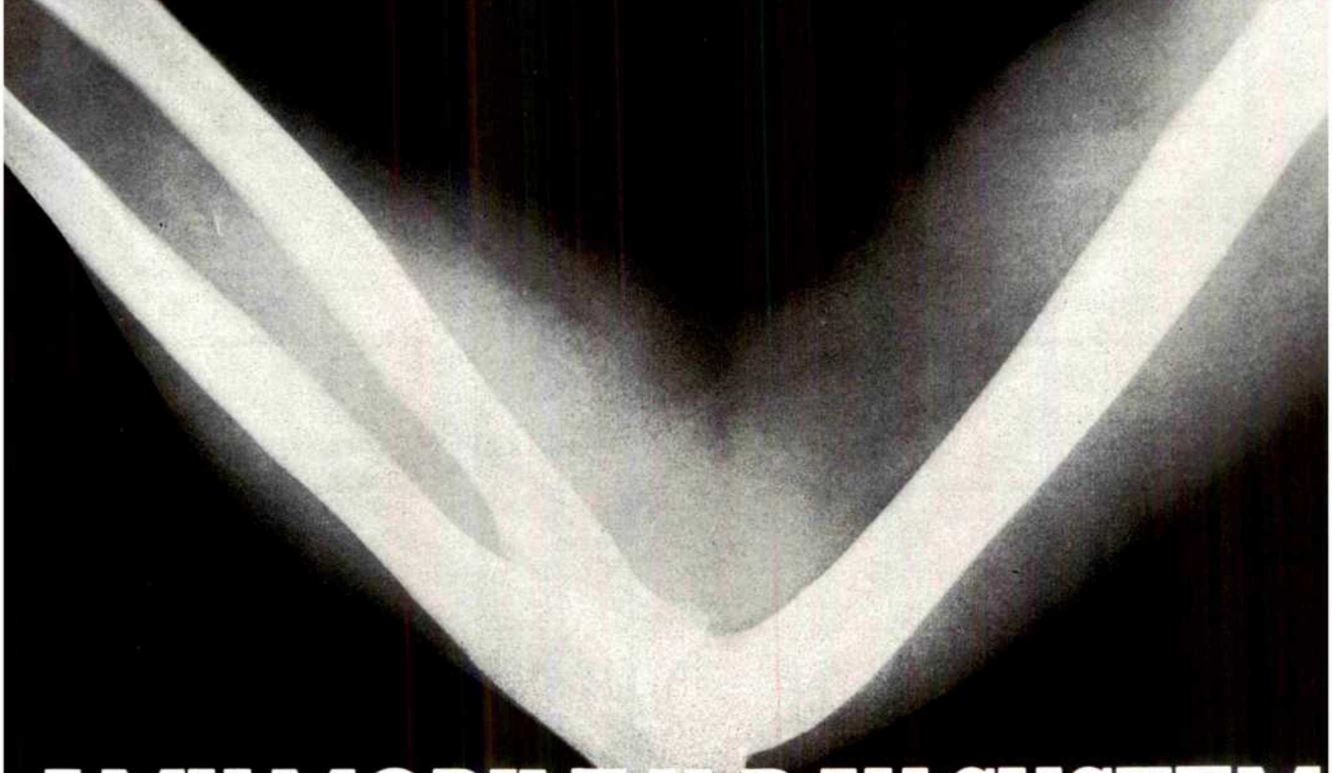

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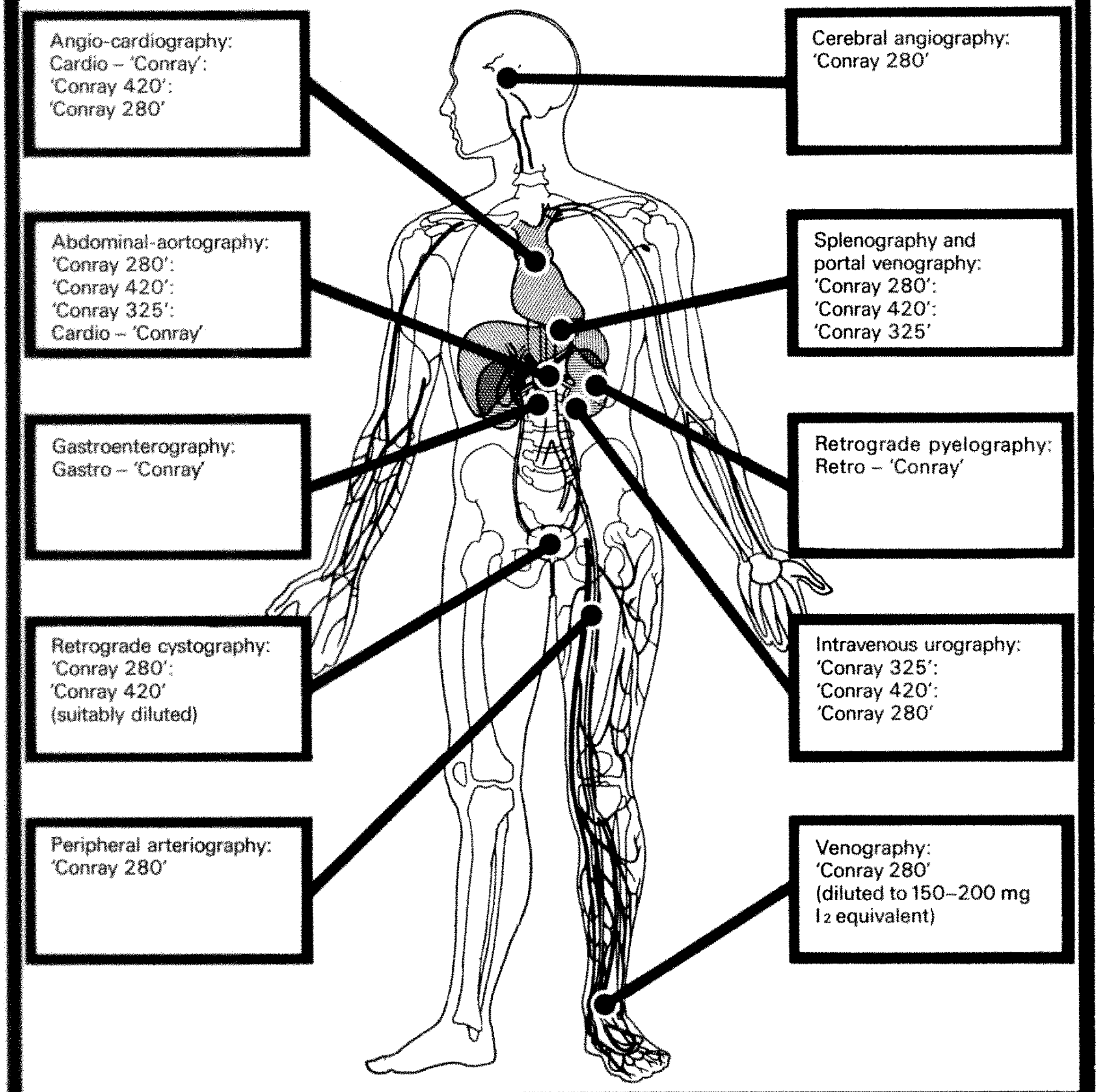

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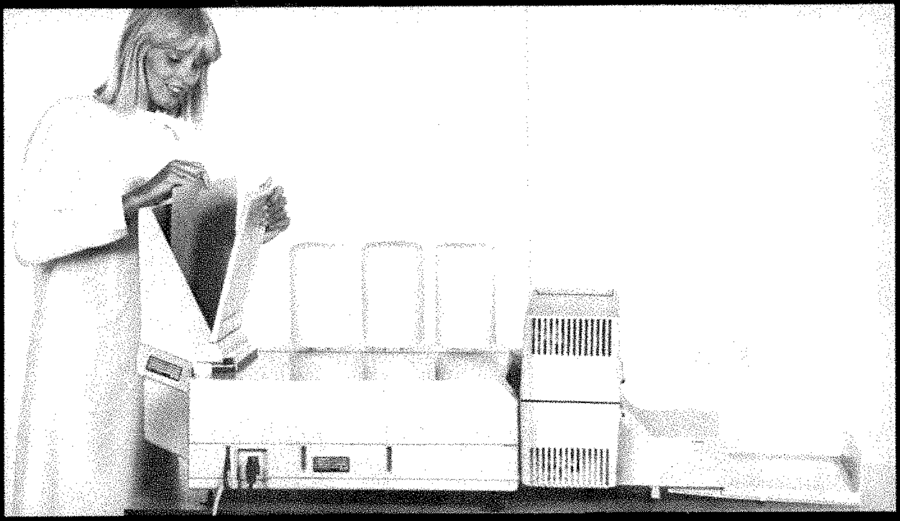

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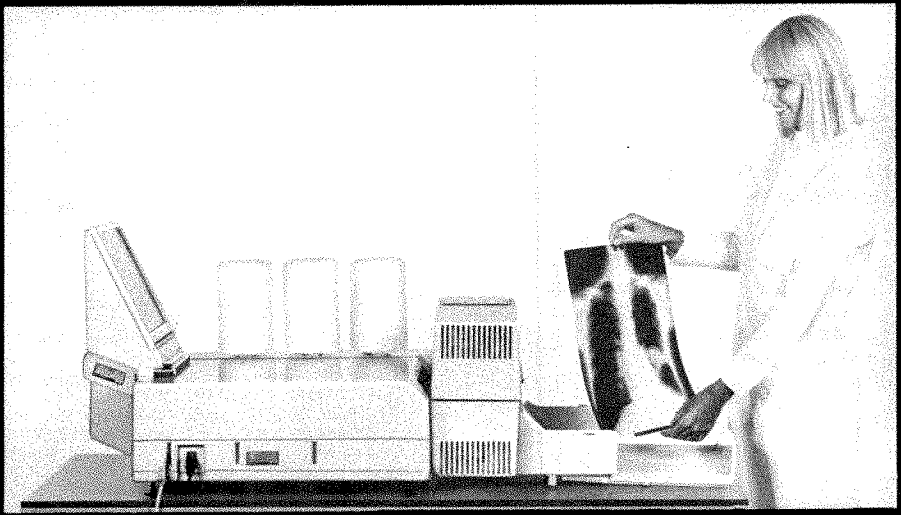

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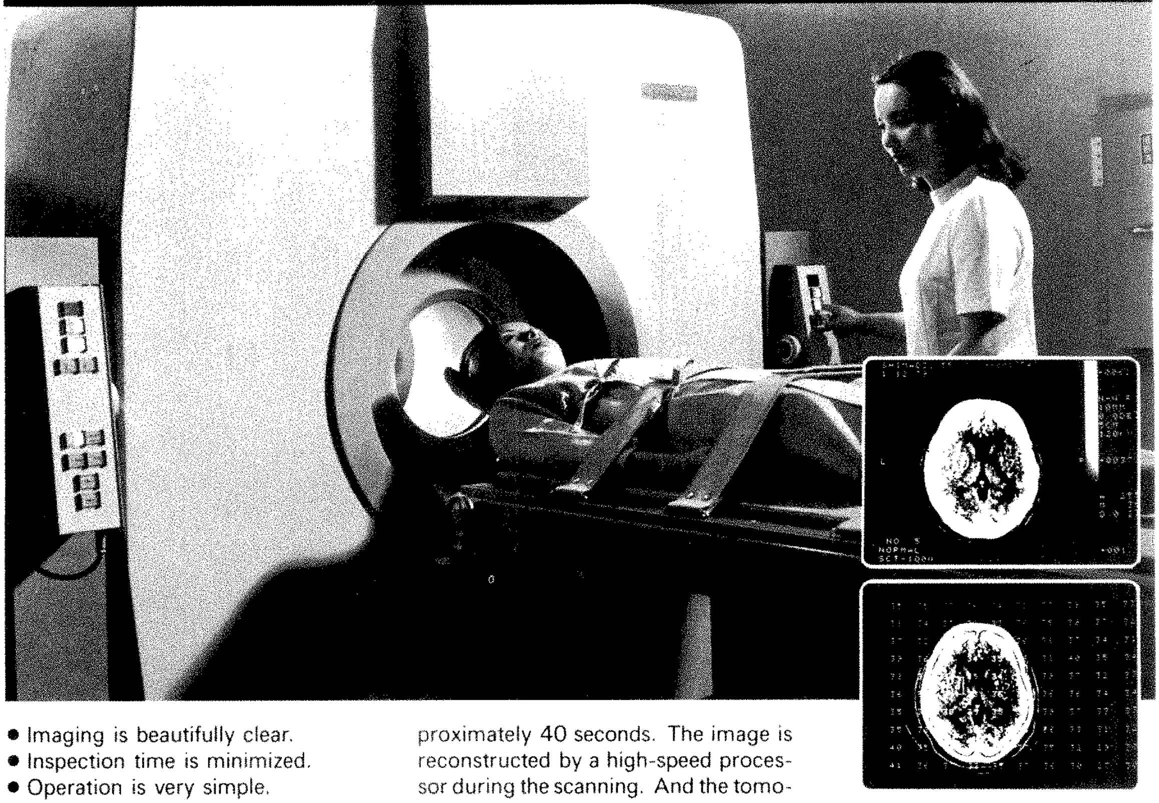

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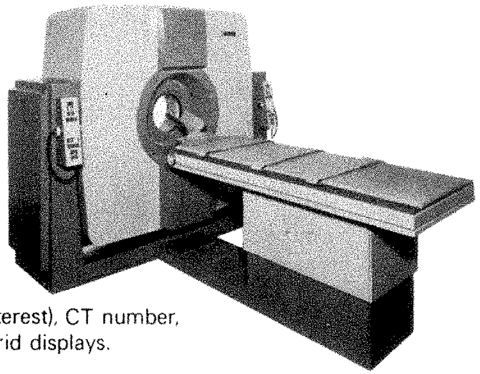

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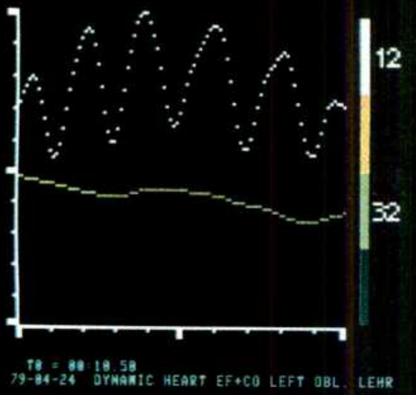

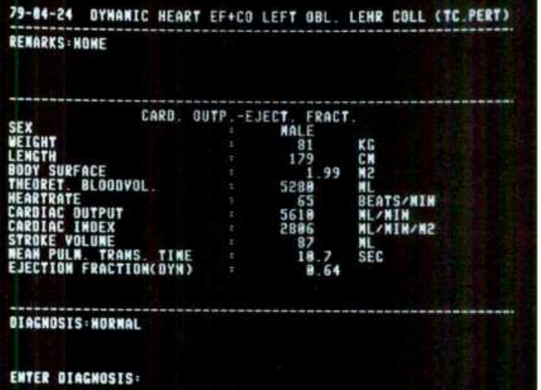

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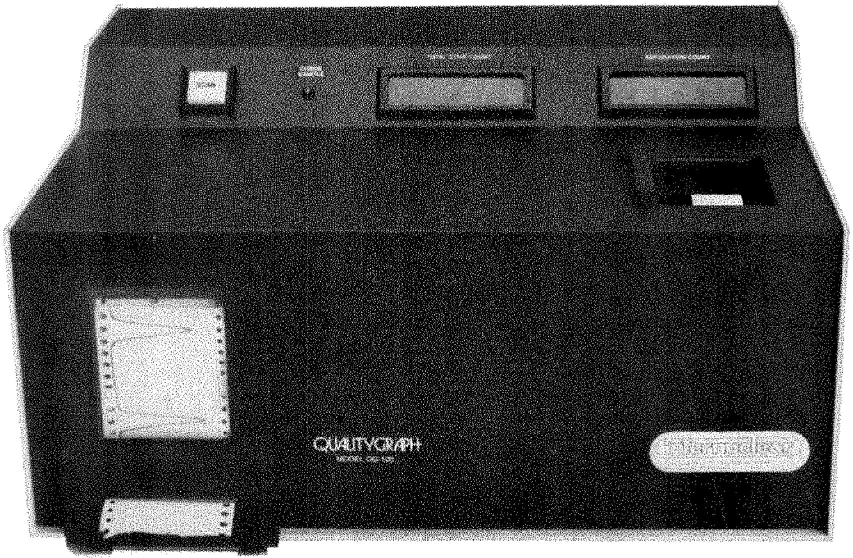

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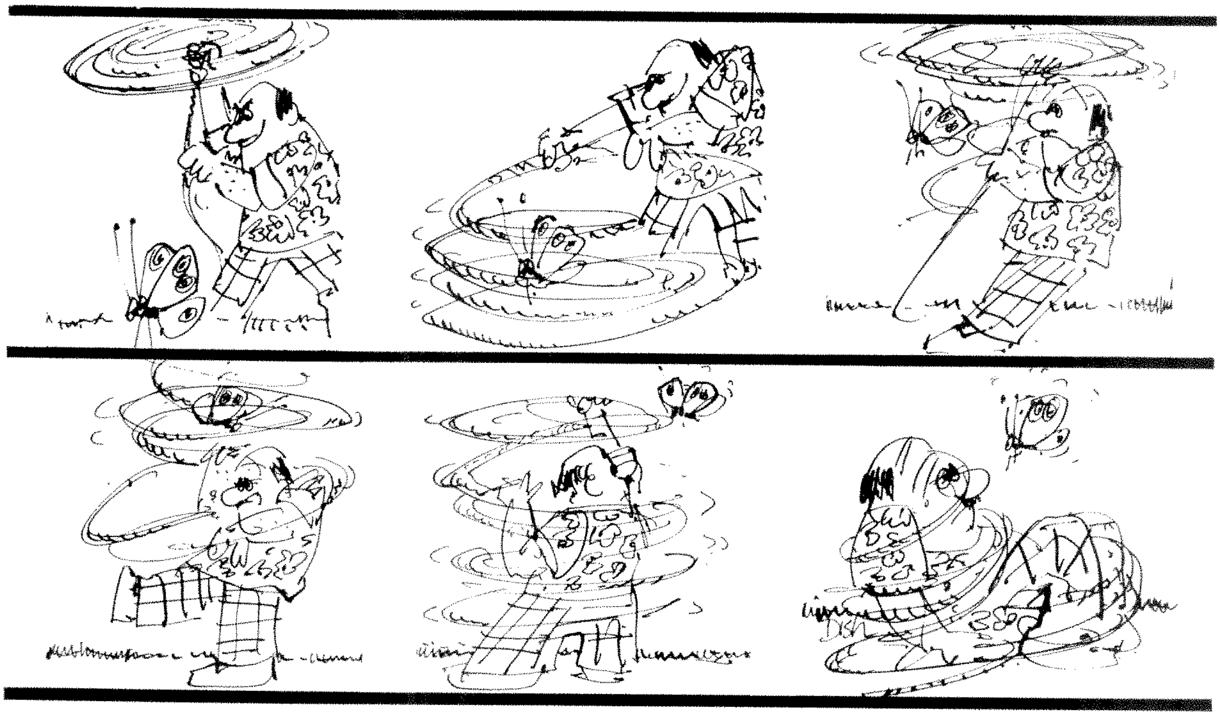

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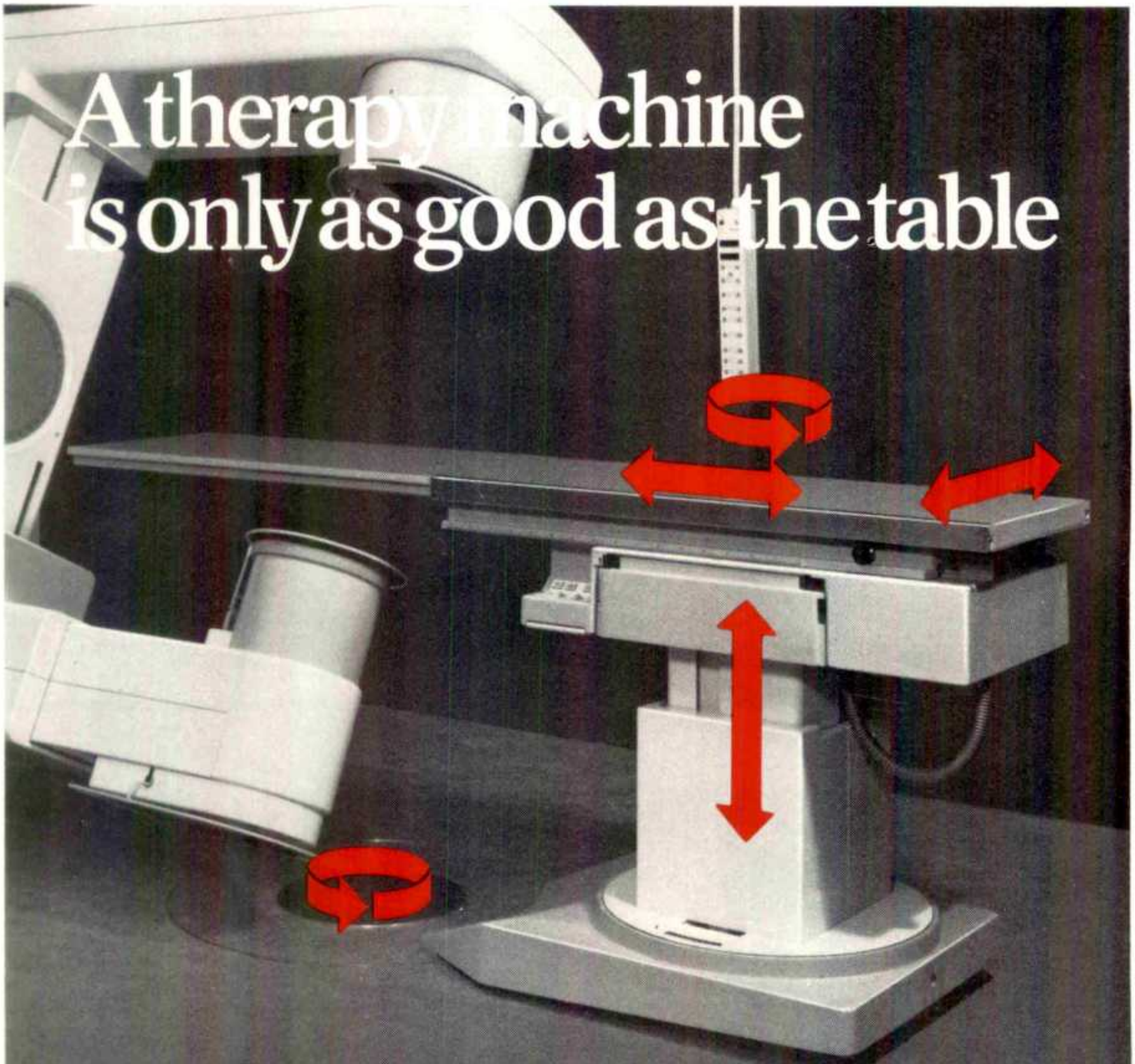

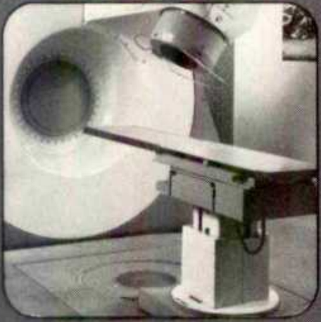

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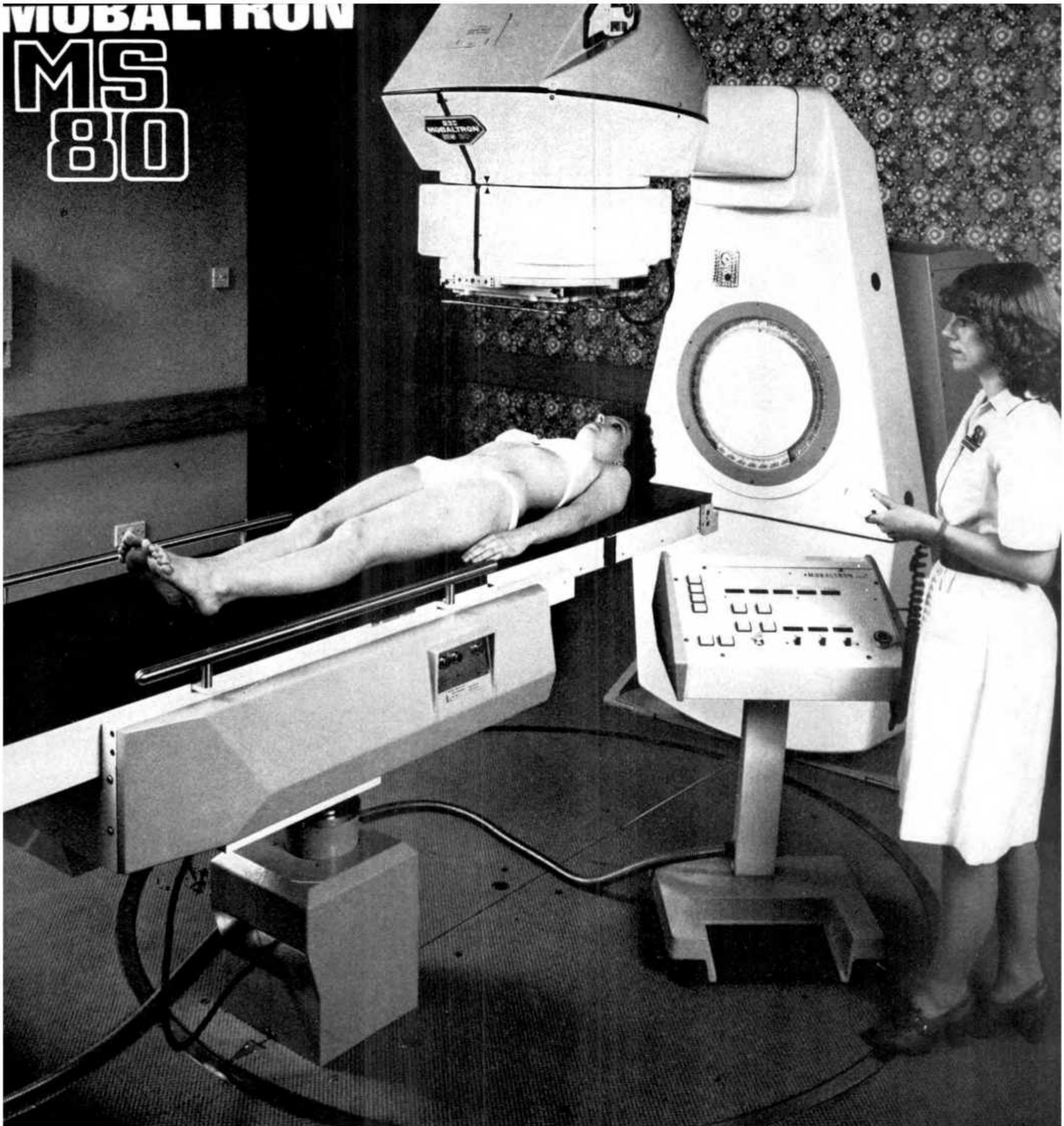

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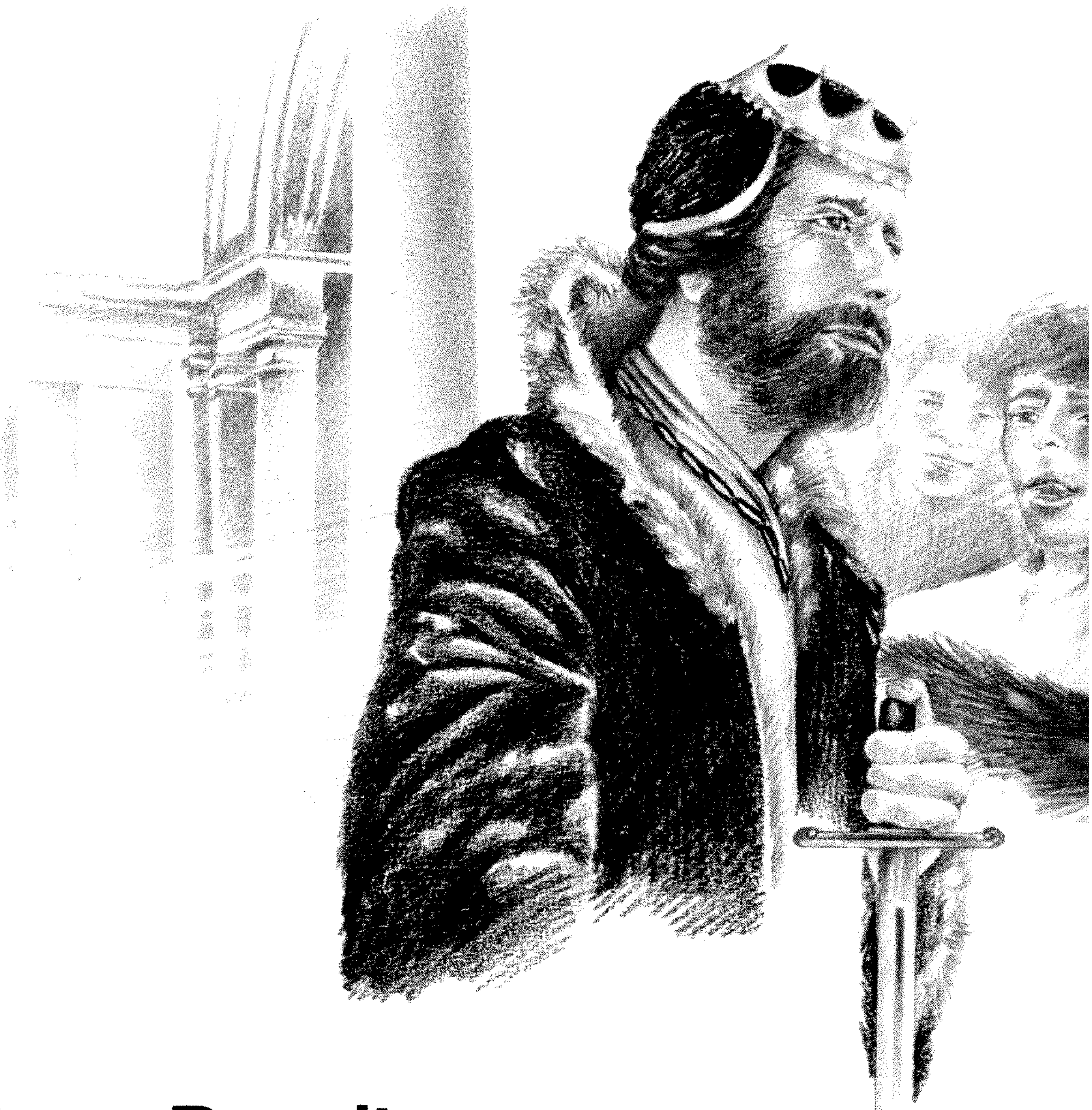

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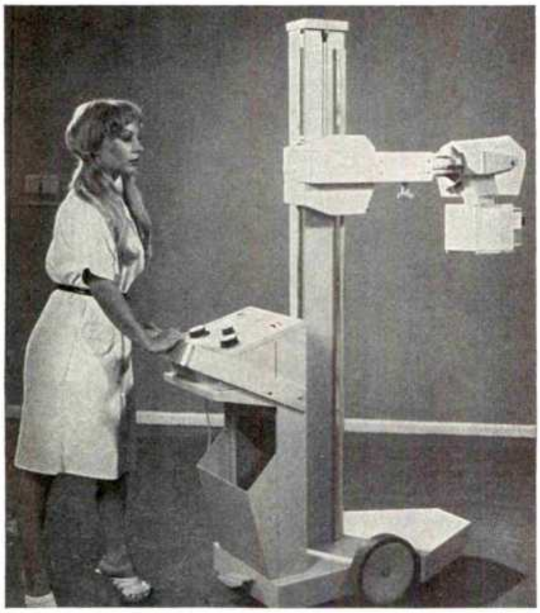

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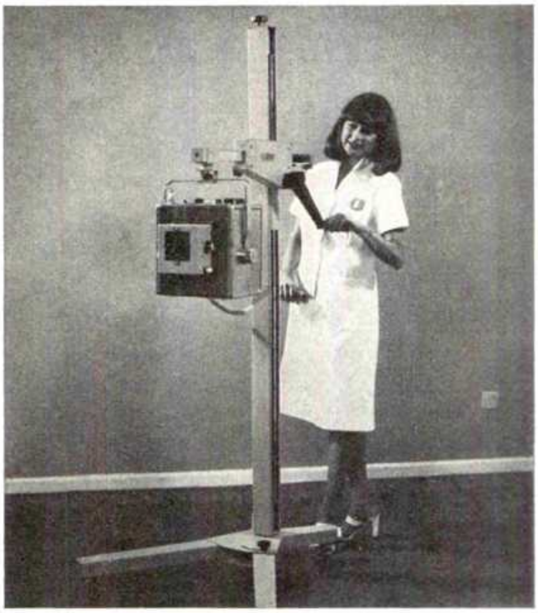

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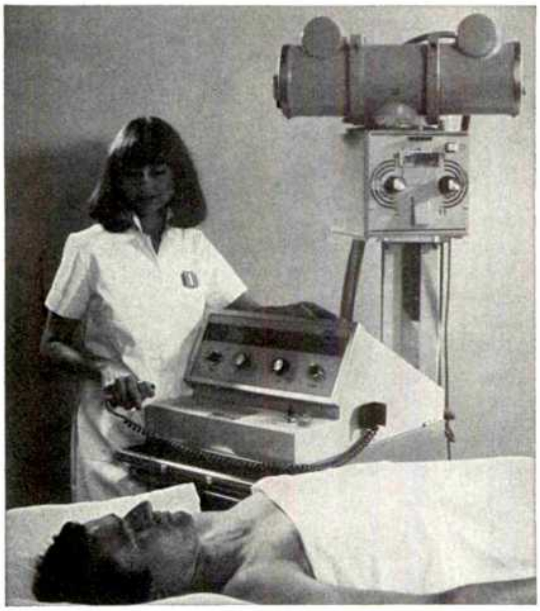

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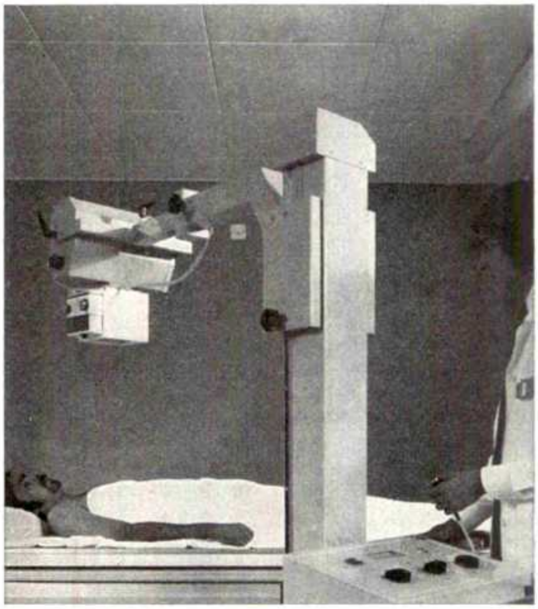

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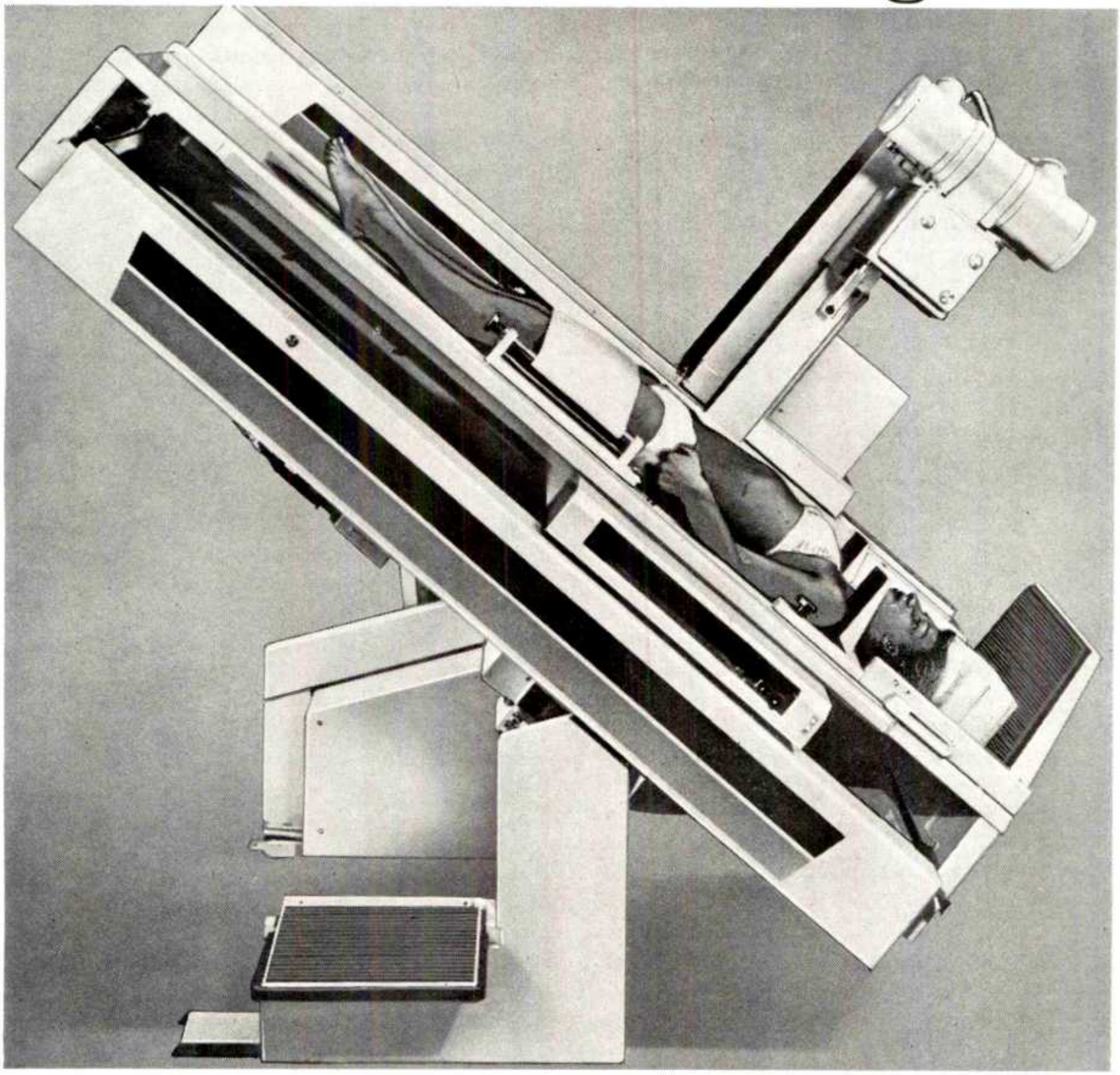

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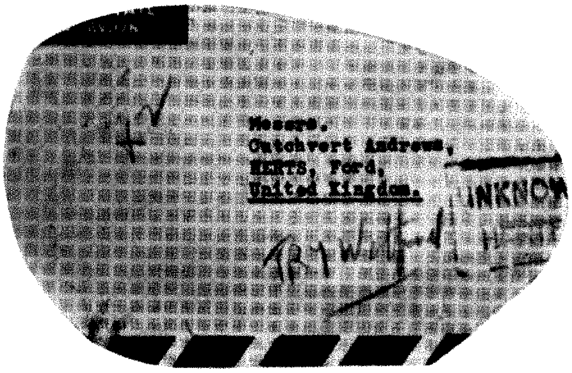

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The British Journal of Radiology

Measuring radiographic bone density and irregularity in normal hands

By F. Paice

Medical Research Council, Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London, W12 0HS

(*Received December 1978 and in revised form May 1979*)

ABSTRACT

This paper describes a method of measuring the radiographic density of the proximal phalanges and metacarpals using a television image analyser. The site for measurement is highly definable and covers the majority of the middle 2/4ths of these bones. Measurements yield two figures; one for mean bone density and one for the density distribution factor (irregularity). Thirty pairs of normal female hands were radiographed and measured. Variations of density and irregularity bone by bone, with age and with dominance are described.

Methods of estimating bone mineral content by radiographic densitometry have been described previously by Keane *et al.* (1959) and by Doyle (1961) using a microdensitometer, by Colbert and Garrett (1969) in conjunction with an on-line computer, by Wing and Birring (1976) using a microdensitometer with special amplifiers, and by others.

A new technique for measuring bone density from radiographs of the hand has been described by Dickson *et al.* (1973). Although not an accurate measure of bone mineral content, it does give an indication of changing bone density. This technique makes use of a television image analyser designed and developed by M. B. Coyne and F. Paice at the Medical Research Council's Cyclotron Unit in London (Coyne 1974). The equipment and technique have been improved, a new measurement of bone irregularity devised, and a more accurate assessment of reproducibility made before this present study on 30 normal hands was carried out. In this equipment a monochrome television camera views the radiograph. The resulting shades of grey in the image are converted by the analyser into seven different colours. These are displayed on a colour television monitor. A calibrating wedge included on the radiograph allows the colours to be adjusted to known densities. Any film-to-film variations in exposure or processing are therefore self-cancelling as they affect the wedge and the hand equally. The analyser can measure the relative area occupied by each colour. Area measurements are restricted to within an electronically generated window. The window is adjusted in height and width to fit the middle 2/4th of each metacarpal and each proximal phalanx.

From the area measurements of known densities, the mean density can be calculated. This figure includes some density contributed by the over- and underlying soft tissue. It is therefore not a precise measurement of bone density alone. However, where the soft tissue component does not change significantly it can be used to measure the relative changes in bone density. The technique was originally developed for studying rheumatoid arthritis where many of the patients have badly deformed and painful hands. In the interest of patient comfort and ease of handling through the X-ray department, it was thought that a dry technique was preferable to water baths which would eliminate the soft tissue variations. For this reason, and because it is not known what the individual variations may be, patient-to-patient comparisons are not normally made. Comparisons are limited to serial radiographs from the same patients.

It was thought that a comparative study under the same conditions on a small group of clinically healthy hands would be useful. A pilot study of this nature should begin to establish the normal range, distribution and variations of bone density. In order to keep variations to a minimum in a small sample, the subjects chosen were all females with the same occupation. To this end 30 typists volunteered to have their hands examined and radiographed.

MATERIALS AND METHODS

Calibrating wedge

The calibrating wedge (Fig. 1) was machined in one piece from an aluminium block. The steps are in an approximately logarithmic progression from 1 to 12 mm. It is tapered, such that it is 1 cm wide at the thin end and 2 cm wide at the thick end. The tread of each step is 5 mm except the last (thickest) step which has a 10 mm tread. Due to X-ray edge effects the periphery of the thicker steps cannot be used. The increased width with thickness allows the central portion of the wedge to be free from these errors.

Radiography

It is essential, of course, that the wedge and the bone being measured should have received the same X-ray exposure. X-ray beams are not entirely uniform, and in order to keep these non-uniformity effects to a minimum only a small portion of a large X-ray field is used. The right and left hand are radiographed separately at 1 m FSD. Apart from the inclusion of the calibrating wedge no other changes were made to the standard radiographic procedures at this hospital. The dose to the hand was approximately 70 mR at 54 kV X-rays, and all other radiographic factors provided they are uniform are self-calibrating against the wedge. In order to further reduce any non-uniformity errors, two identical wedges are used, one on the radial and the other on the ulnar side of the hand. During analysis, the radial and ulnar half of the hand are compared with their respective wedges. Thus, the bone being analysed is never more than 6 or 7 cm away from a calibrating wedge. Comparison of the two wedges will give an indication of any variation across the film. The wedges are cemented onto a Perspex film cassette carrying plain envelope wrapped film. This ensures that the wedges are correctly positioned and cannot be inadvertently omitted.

Marking off

The middle 2/4ths of each metacarpal and each proximal phalanx are indicated by two small pencil points. The upper and lower limits are found using a simple grid (Fig. 2). On an X-ray viewer, the radiograph is superimposed over the grid, whilst keeping the bones parallel to the vertical guide lines. The two extremities of the bone are positioned on the two outside lines, the middle 2/4ths are then marked off using the two inside lines. The narrowest part of the bone defines the maximum width of the electronic window and the pencil points the height. This site is particularly easy to define and repositional errors are very small.

TV image

The signal from the television camera is rigidly clamped and there is virtually no "DC shift" (an overall shift in image brightness depending on average scene brightness). Once the colours have been assigned to particular steps on the wedge they remain locked to their respective densities even when the remainder of the scene changes over a wide range of brightness. Any overall shift of image brightness and/or contrast can only be attributed to flare within the camera and camera lens. This can be reduced to a minimum by ensuring that the lens is kept perfectly clean, and by the use of a mask of sufficient size to just accommodate the largest metacarpal. This ensures that no unnecessary light enters the camera lens.

Measurement

The radiograph is placed over the illuminated

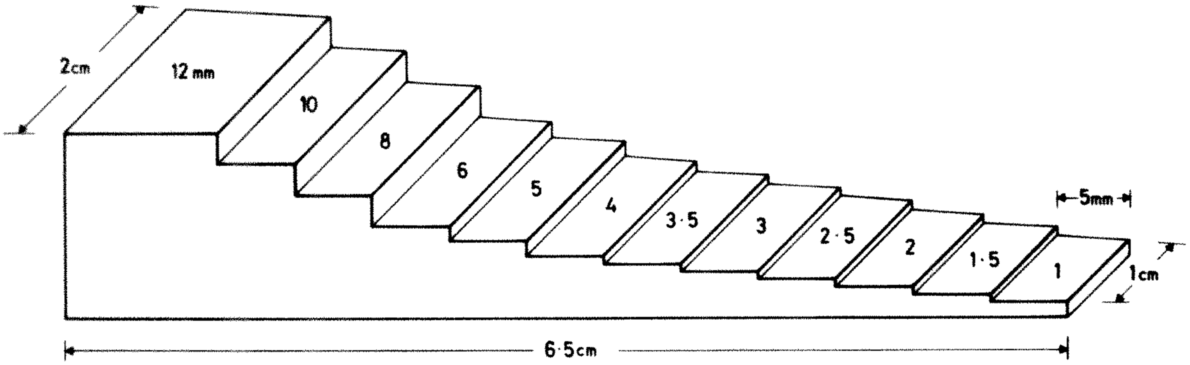

FIG. 1.

The aluminium calibrating wedge.

aperture and the wedge viewed by the monochrome camera. The shades of grey are then translated into various colours, and adjusted to occupy the appropriate steps on the wedge. The colours are adjusted, so that each is just on the point of changing to the next lower (thinner) step on the wedge. This ensures that the colours are set accurately and reproducibly. Having "tuned" the wedge the first bone is positioned over the aperture and the electronic window set to produce the largest rectangle that can be accommodated within the middle 2/4ths of the bone. Each colour is measured in turn and a reading is printed, which is proportional to the area occupied by that colour within the window.

As the window is fully occupied by colour, the sum of these numbers (Σ_n) is proportional to the window area. Each colour represents a certain thickness (t) of aluminium. Therefore, the mean bone density covered by the window can be expressed as equivalent to a thickness of aluminium ($\bar{t}$) where $\bar{t}$ is given by:

$$\bar{t} = \frac{\Sigma(n.t)}{\Sigma(n)}$$

It is possible, of course, to have two bones with the same mean density, but covering quite a different spread of densities (Fig. 3). A method of expressing this spread may be given by "density distribution factor" (DDF) of equivalent thickness of aluminium using the following formula:

$$\text{Density distribution factor } \sigma = \sqrt{\frac{\Sigma[n(t-\bar{t})^2]}{\Sigma(n-1)}}$$

i.e. an estimate of the standard deviation as calculated for grouped data.

Reproducibility

The reproducibility of the technique was tested to find the magnitude and source of errors.

Included on most radiographs is a standard bone set in a wax block. Ten radiographs were selected, taken on four different dates over a six week period.

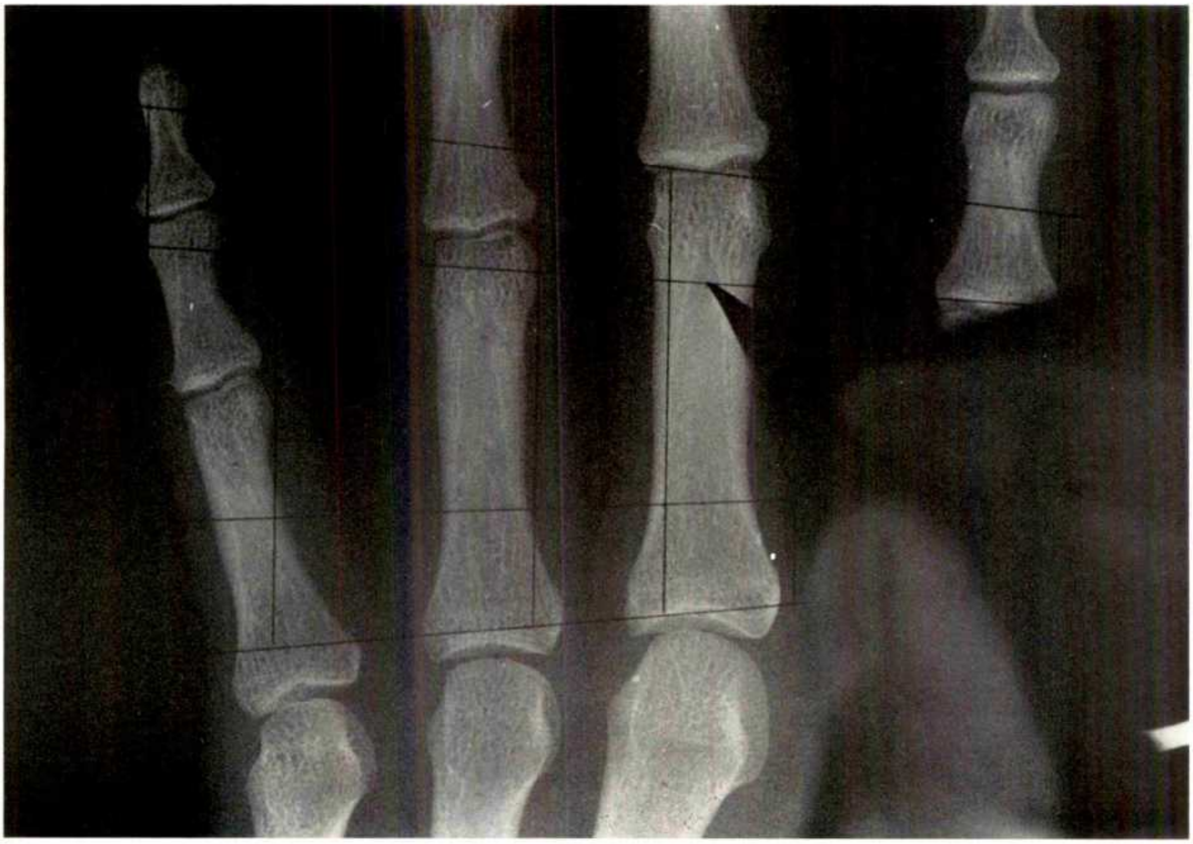

FIG. 2.
Marking off the middle 2/4th of each bone.

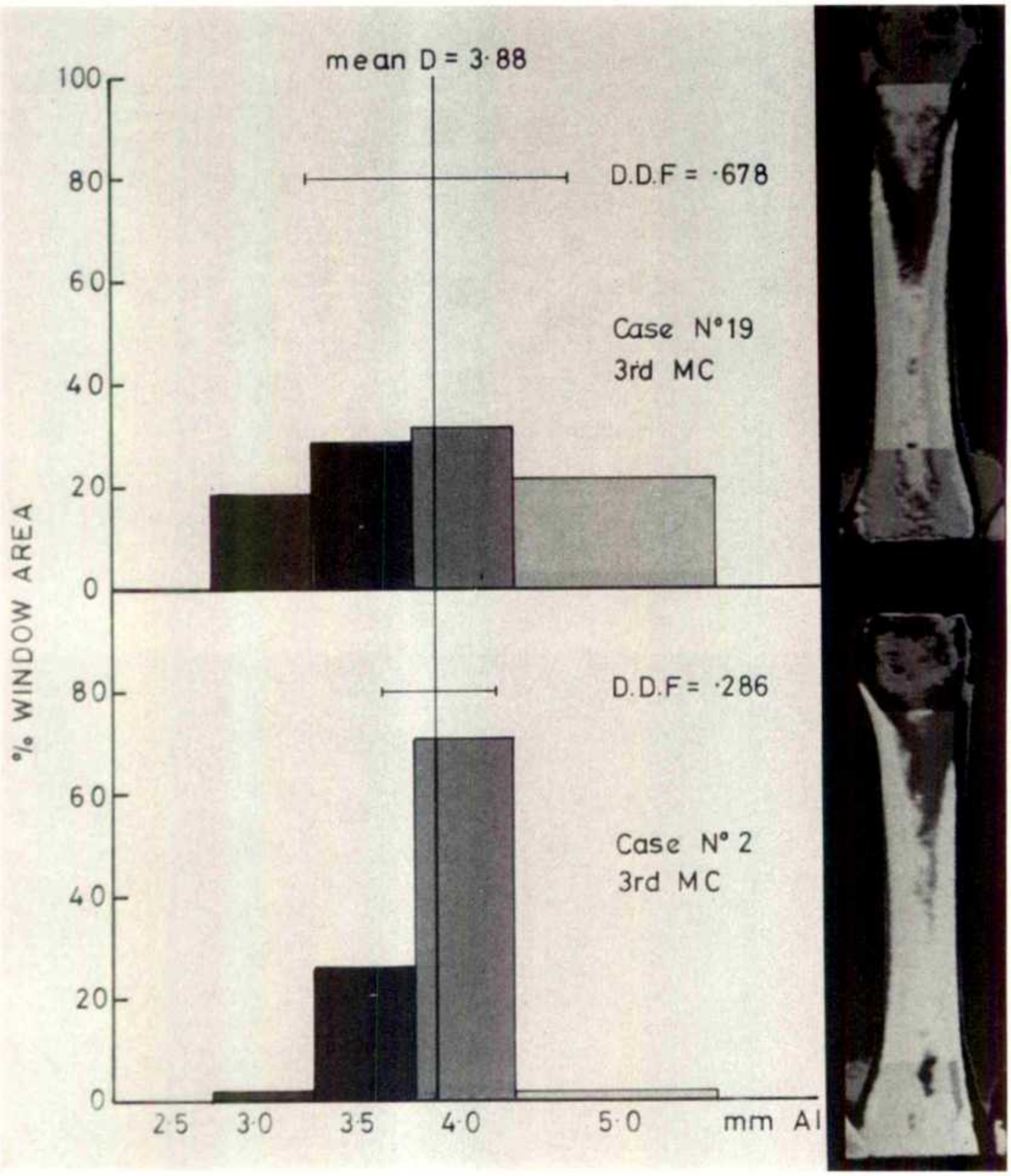

FIG. 3

Two similar bones of the same mean density, but with different distributions.

This should give a reasonable variation of radiographic technique and processing. The mean density of each standard bone was calculated and this gave a coefficient of variation of 1.85%. Eleven repeat measurements on the same radiograph, retuning the wedge and resetting the window each time, gave a coefficient of variation of 0.55%. Eight consecutive measurements on the same radiograph without resetting gave a coefficient of variation of 0.1%.

OBSERVATIONS

The mean bone density and density distribution factor for each bone, the means (density and DDF) for each digit and the means for each hand of our 30 volunteers were calculated. From these results the following observations were made.

Range of bone density

The ranges of the mean bone densities were found

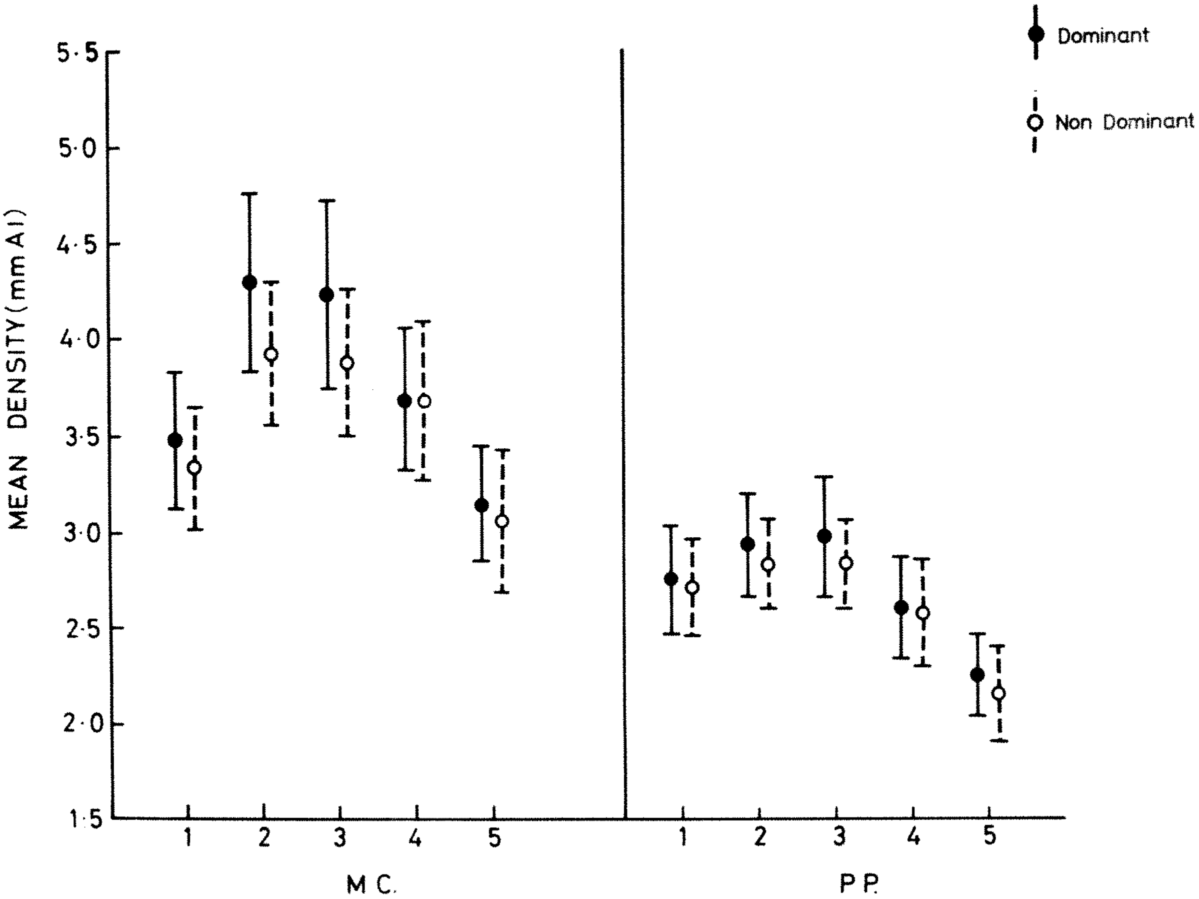

FIG. 4.

The mean bone density and standard deviation (30 subjects) for the metacarpals and proximal phalanges of the dominant and non-dominant hands.

to lie between 1.60–3.51 mm Al for the proximal phalanges (PPs) and 2.25–5.19 for the metacarpals (MCs).

Order of bone density

In most subjects the index (2) or the middle (3) digits were the most dense, followed by the ring (4) or the thumb (1), with the little finger (5) being the least dense (four permutations). Approximately 70% of the PPs fell in the order 2, 3, 1, 4, 5 (32%) or 3, 2, 1, 4, 5 (38%). No PPs of the dominant hand fell in the order 2, 3, 4, 1, 5 in contrast to the MCs which have a great affinity for this order (60%). When the PPs and MCs are combined to find the mean for each digit the distribution is almost uniform throughout the four patterns.

The mean range of densities in each bone

The mean density (30 subjects) and standard deviation for each of the MCs and PPs of the dominant and non-dominant hands is shown in Fig. 4. It can be seen that, on average, all the bones of the dominant hand are more dense than the bones of the non-dominant hand. The second and third digits contribute the major part of this difference.

Variation of density with age and dominance

The mean hand densities for the dominant relative to the non-dominant hands are plotted in Fig. 5. Only in three subjects is the non-dominant hand more dense than the dominant, as indicated by the three points below the line.

The mean hand density over the whole age range, rises to a barely significant degree ($P = 0.05$) for the dominant hand (Fig. 6), whereas there is no significant overall rise in the non-dominant hand. However, there is a rise in both hands between the ages of 20 and 35 years. This suggests that both hands tend to

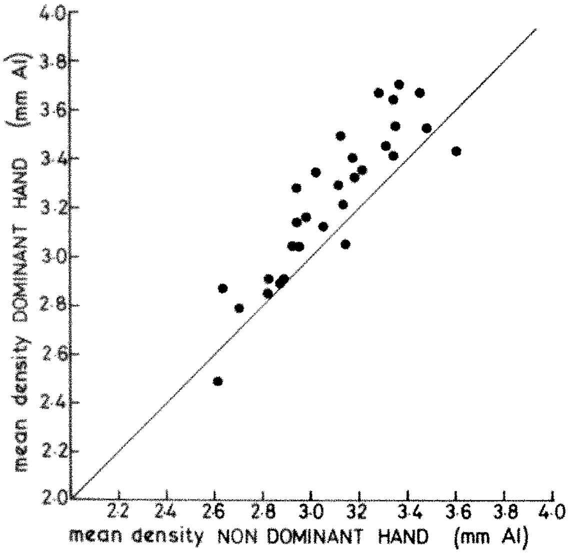

FIG. 5.

The mean hand (ten bones) density showing the relationship between the 30 dominant and non-dominant hands.

rise in density initially, but that in middle age the rate of rise becomes less in the dominant hand and that there is probably a slight fall in the non-dominant hand. The statistics of the older age group are poor, and preclude any analysis more detailed than this type of generalization.

The ratio between pairs of dominant and non-dominant hands shows clearly in Fig. 7. Although the ratio varies considerably (between —4% and +12%) it does rise significantly ($P=0.02$) with age. This effect can be studied bone by bone by re-plotting Fig. 4 for two age groups (< 35 and > 35) as in Fig. 8. It can be seen that, on average, all the bones of the dominant hand except MC5 are denser in the older group, but that there is much less change in the bones of the non-dominant hand.

The mean range of the density distribution factor in each bone

Turning now to DDF measurements we find the mean for all the bones (Fig. 9) gives a very similar

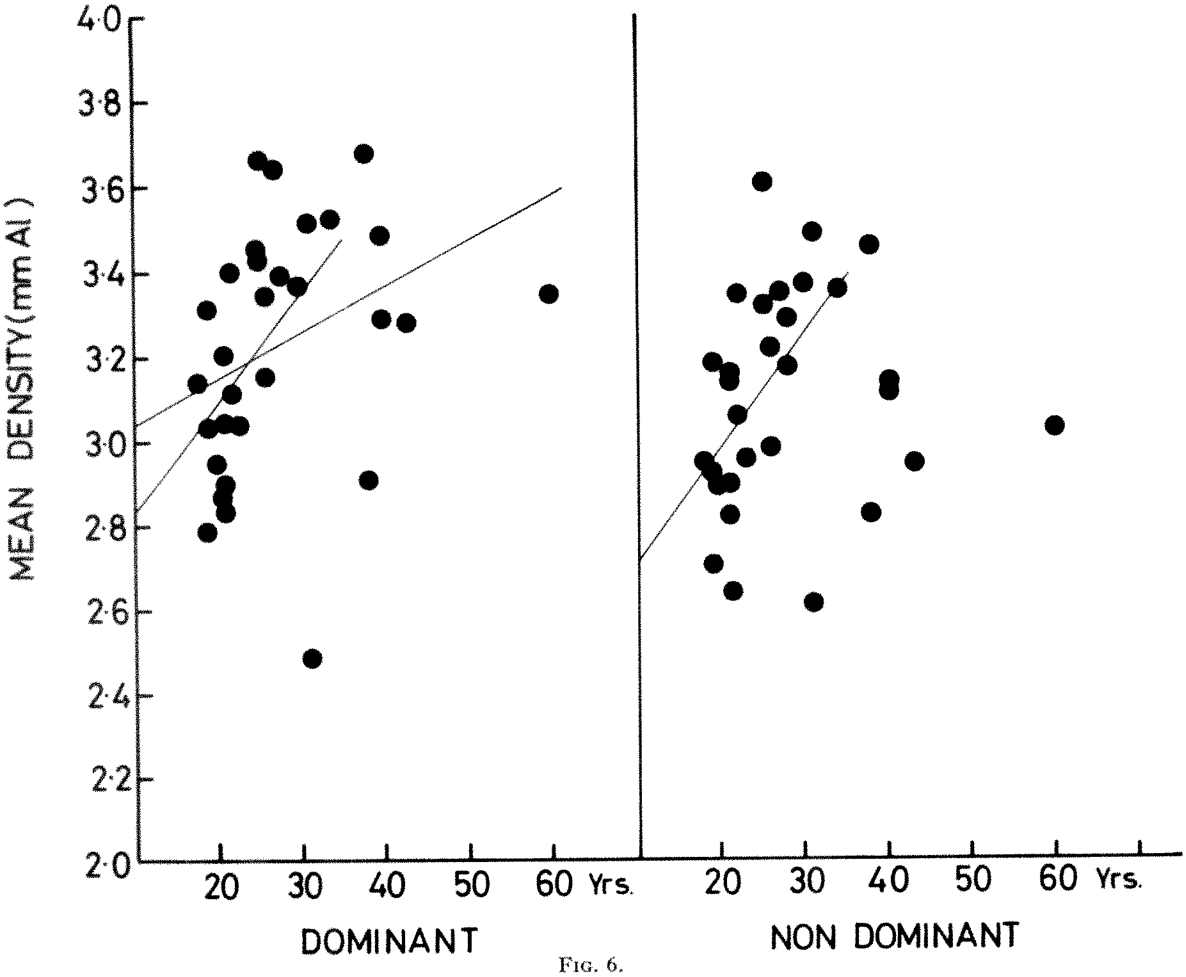

FIG. 6.

The mean hand density for 30 dominant and non-dominant hands plotted against age.

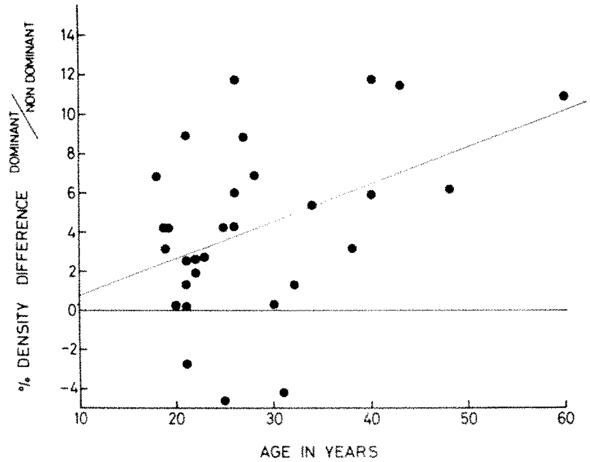

FIG. 7.
The ratio between pairs of hands expressed as a percentage plotted against age.

picture to the density measurements. The majority of the bones of the dominant hand seem more irregular (higher DDF) than those of the non-dominant, particularly the second and third MC. The proximal phalanx of the thumb is also notable for its irregularity.

The variation of DDF with age and dominance

Mean hand DDFs plotted against age (Fig. 10) shows that the DDF rises significantly with age ($P=0.02$) but unlike density does so about equally in both hands. Again a steeper rise is seen in the younger age group. The bone-by-bone effect for the two age groups can be seen in Fig. 11. Only MC1 in the non-dominant hand seems not to follow the generally equal upward trend. It was found that three subjects (but not the same three as in Figs. 5 and 7) had higher DDFs in the non-dominant hand. The

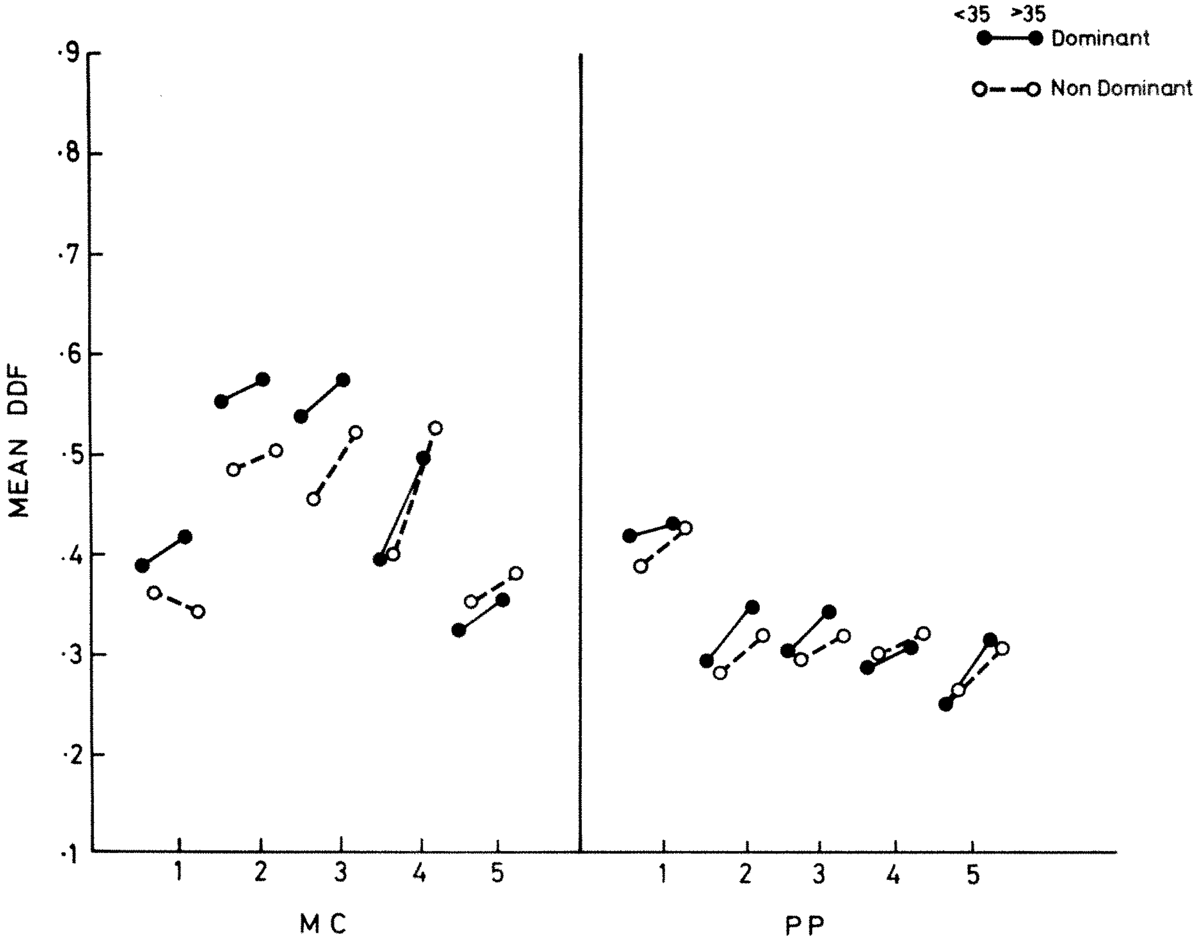

FIG. 8.
The mean bone density (30 subjects) of the metacarpals and proximal phalanges when divided into two age groups <35 and >35.

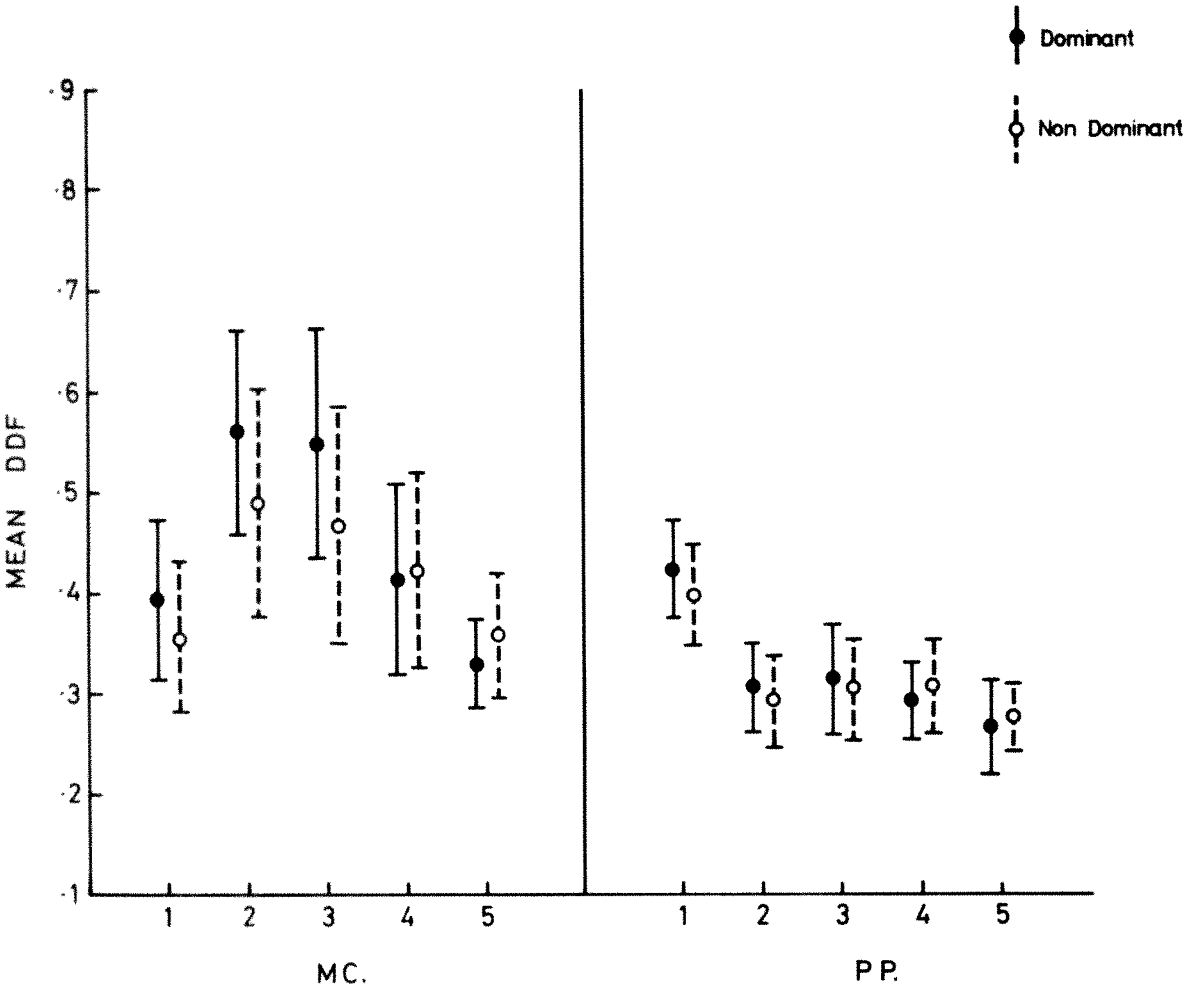

FIG. 9.

The mean bone DDF and standard deviation (30 subjects) for the metacarpals and proximal phalanges of the dominant and non-dominant hands.

ratio between pairs of dominant and non-dominant hands varied between —6% and +30% but it was not possible to fit a regression line to a plot of the ratios confirming that both hands increase about equally.

The relationship between density and DDF

The relationship between density and DDF for all 600 bones measured is shown in Fig. 12. Although density and DDF rise approximately together there is a large latitude and a high DDF does not necessarily result from a high density. Superimposed over this scattergram are the limits imposed by one standard deviation from the mean for each bone of the dominant hand only and it is therefore a combination of Figs. 4 and 9; the greater irregularity of PP1 separates it well from the other bones. MC2 and MC3 are also notable for their high density and DDF.

CONCLUSIONS

The measurements which were made of density and DDF are a pilot study to see if any patterns emerge from a group of female typists with clinically normal hands. As it turned out the group contained few subjects over 35 years of age. This made the statistics above that age rather sketchy. It was not possible to detect any difference between those using electric as opposed to manual typewriters. Certain patterns did, however, emerge as follows:

(i) The density and DDF were highest in the 2nd and 3rd digits.

(ii) The density and DDF were higher in the

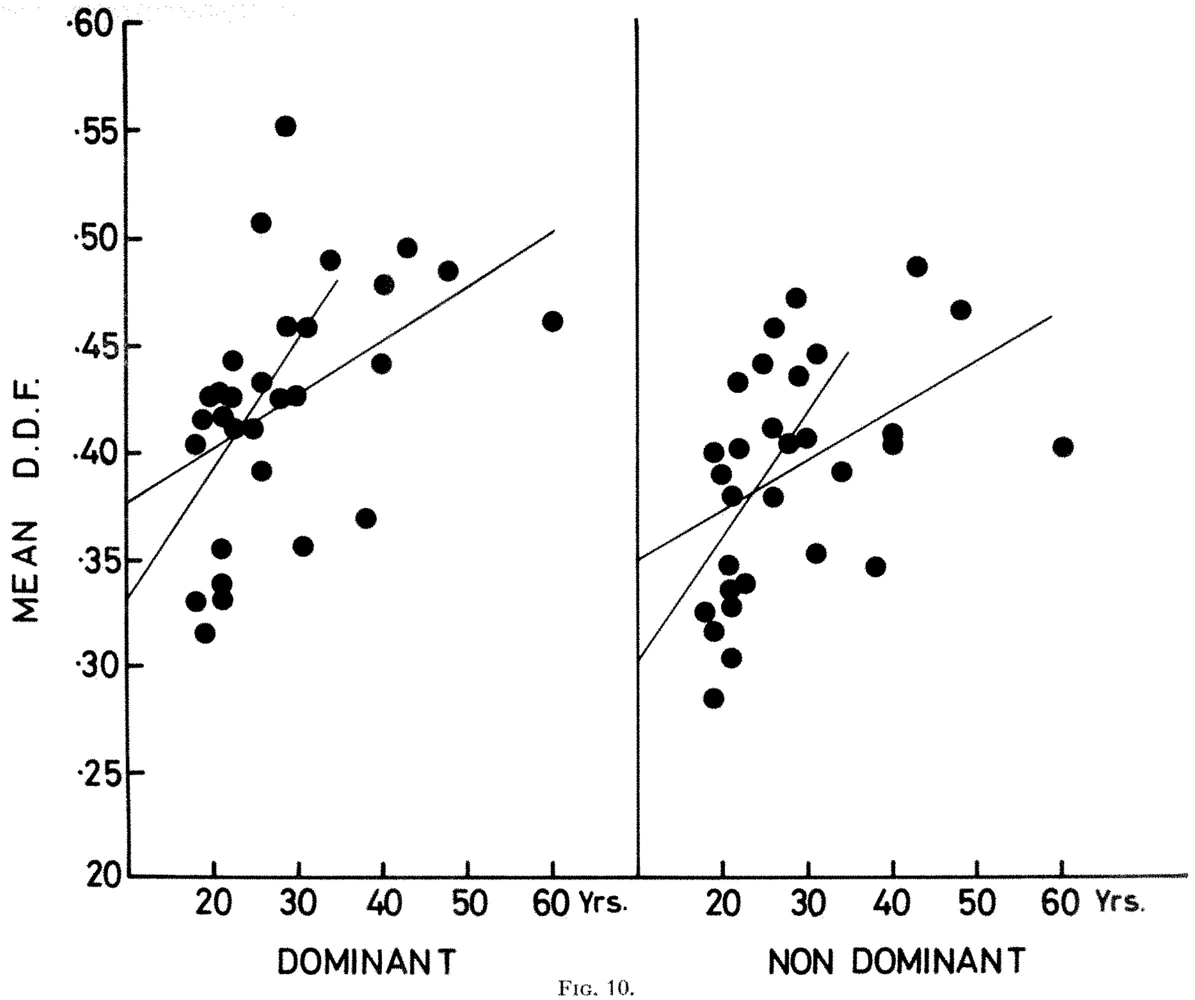

Fig. 10.
The mean hand DDF for 30 dominant and non-dominant hands plotted against age.

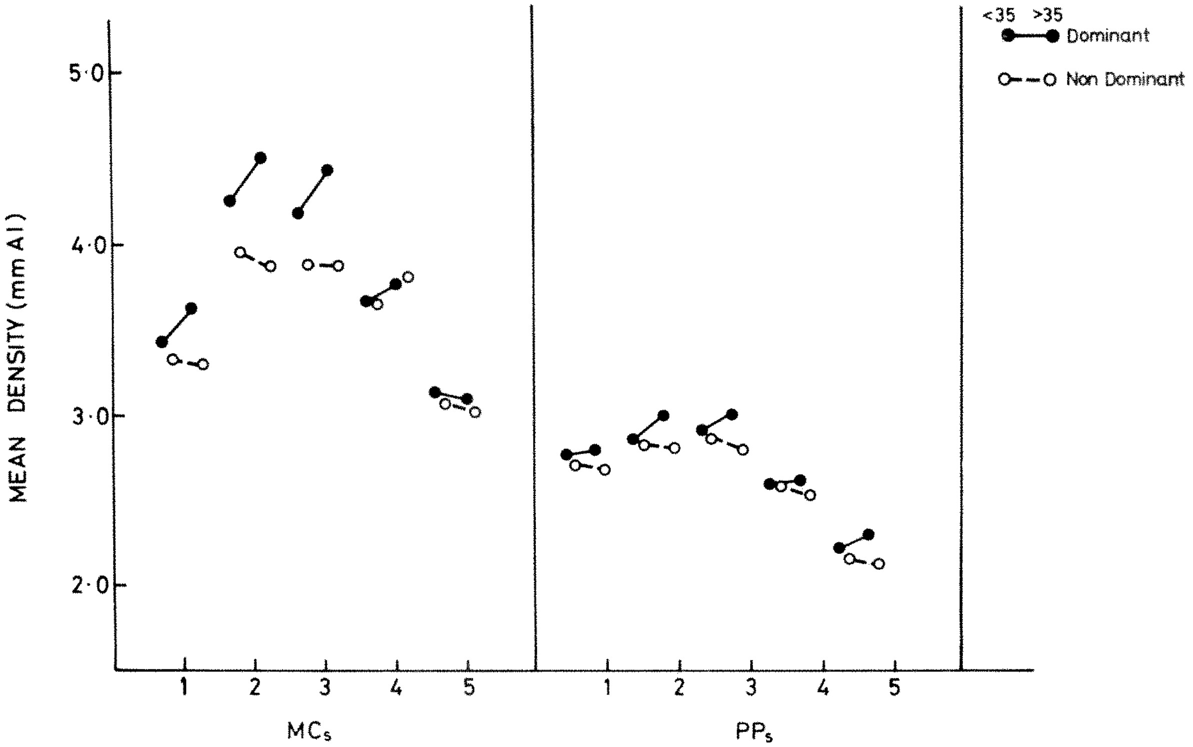

Fig. 11.
The mean bone DDF (30 subjects) of the metacarpals and proximal phalanges when divided into two age groups <35 and >35.

dominant hand in 80% of the subjects, and in no case were both density and DDF lower in the dominant hand.

(iii) The density of bones appears to rise with age and to continue to do so in the dominant hand, while in the non-dominant hand it may stabilize or begin to fall slightly in middle age.

(iv) The second and third digits contribute the major part of the difference between the two hands.

(v) The DDF also seems to rise with age, but does so about equally in both hands.

The ranges and patterns which have emerged are not random but tend to follow definite lines. It may be desirable to extend our knowledge of normal hands by adding to and thereby improving the statistics of this group of female hands and also to study groups of male sedentary and male manual workers.

Although the over- and underlying soft tissues contribute to the density and DDF measurements, particularly of the metacarpals, it was felt that the measurements were a valid description of the general condition. The major part of this description is of bone density and serves to quantify the image that the radiologist normally assesses visually.

The technique submitted here is relatively simple, requiring no great skill or vastly complicated equipment if access to a suitable image analyser is available. Neither does the technique cause any great inconvenience to the X-ray department or the patients. The analysis is reasonably quick; on our instrument three patients (60 bones) could be analysed in one hour.

The image analyser we have used is one of two made by the MRC, the other being at the Welsh National School of Medicine, Cardiff. Other similar instruments are available commercially, mainly for

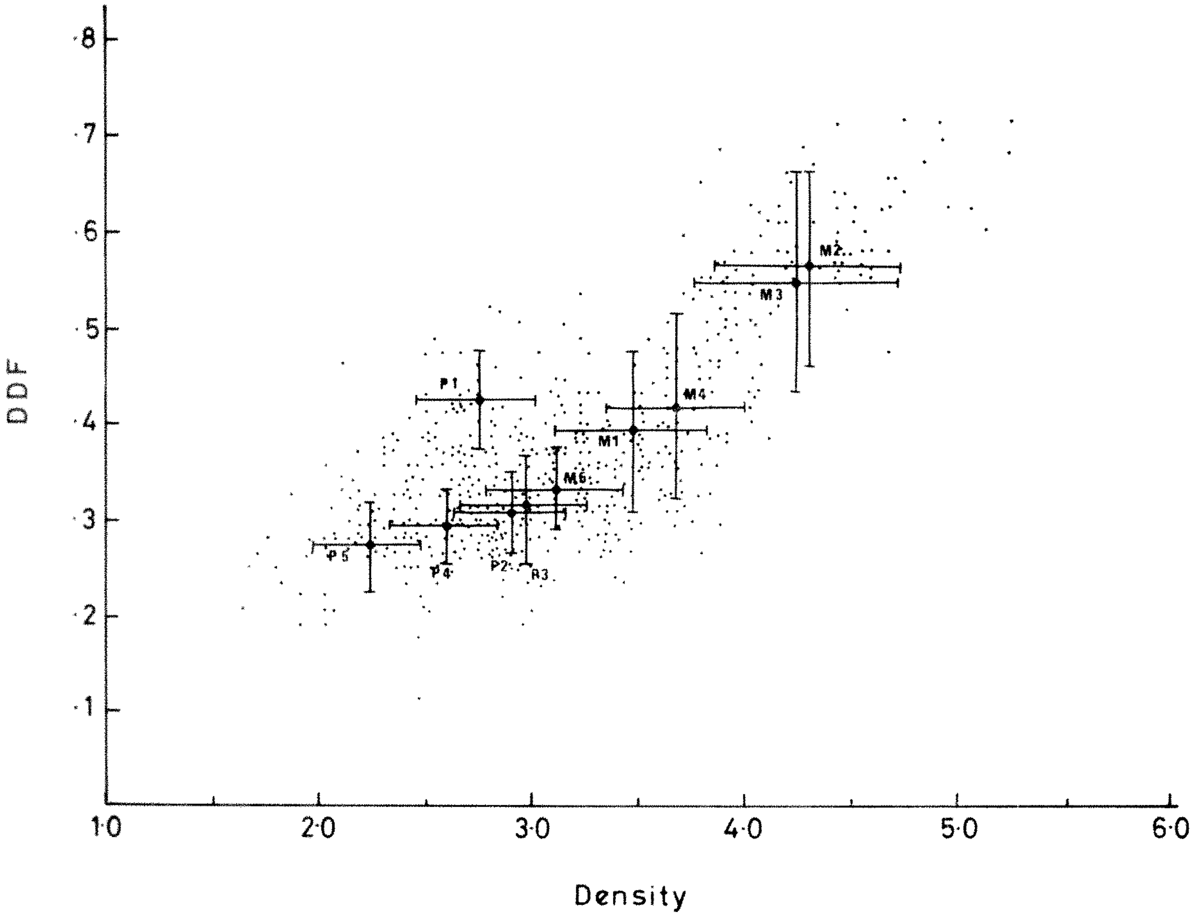

FIG. 12.

The relationship between bone density and DDF for all 600 bones showing, within one standard deviation from the mean, the positions of the bones of the dominant hand.

use with microscopes, but should be adaptable for viewing radiographs.

ACKNOWLEDGMENTS

The author would like to thank Mr. S. Tandon of the Royal Postgraduate Medical School for his help in arranging for the radiography and for assessing the clinical condition of the hands, and the staff of the X-ray Department, Hammersmith Hospital for their co-operation.

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Book review

Medical Imaging. A Basic Course. Edited by Louis Kreel with a foreword by Professor R. E. Steiner, pp. viii+256, 330 illus., 29 tables, 1979 (H. M. & M. Publishers Ltd., Aylesbury, Buckinghamshire), £18·00.
ISBN 0-85602-069-9

It is now 84 years since Dr. Wilhelm Conrad Röntgen discovered X rays. In that time conventional diagnostic radiology has established itself as an acceptable and very reliable imaging method and many would consider its position in this respect unassailable. In spite of this, such has been the impact of the introduction of the three newer imaging methods, computerized tomography (CT), ultrasound (US), and isotopes (IS) that in this book on medical imaging, conventional radiology hardly gets a mention. The aim of the book is to provide a basic text which records the available experience at the present time in the three different scanning modalities: computerized tomography, ultrasound and isotope imaging. A short chapter describing nuclear magnetic resonance has also been included. The production of the book was stimulated by the British Council course on medical imaging held in 1977 at Northwick Park Hospital and Clinical Research Centre, Harrow.

The book is produced primarily for radiologists. It sets out to provide a comprehensive cover of the main topics from experienced workers in each field and to be sufficiently clear and detailed so that it can act as a practical guide to the theory, equipment and science of the various scanning techniques. It succeeds admirably in this aim so far as CT is concerned (156 of the 240 pages of text are devoted to CT) but it is much less successful with ultrasound (51 pages). Isotope imaging gets scant treatment (only 13 pages). The 24 contributors are all experts in their field. CT is comprehensively described and beautifully illustrated; for this alone the book is valuable.

The text is presented in eight parts. Section 1 covers the theory, technical aspects and equipment of CT, ultrasound, isotopes and nuclear magnetic resonance imaging, zeugmatography. Section 2 describes and illustrates the normal axial anatomy of the brain, skull, thorax, abdomen and pelvis. Section 3 deals with patient preparation and contrast medium enhancement in CT. Section 4 is on CT of the head and it includes a short description of ultrasonography of the orbits. Section 5 covers CT of the body including the thorax, liver, pancreas, kidneys, lymph nodes, retroperitoneum and pelvis and the applications of CT in radiotherapy. This section ends with a short chapter on the place of ultrasound and CT in oncology. Ultrasonography finds a place in Section 6. This section ranges relatively superficially compared with the previous sections on CT, through obstetrics, the liver and pancreas, urinary tract, retroperitoneum and pelvis, miscellaneous uses of ultrasound and echocardiography. Some of the clinical uses of isotope imaging comprise Section 7 and in Section 8 comparison is made between the value of CT and ultrasound of various organs.

Dr. Kreel and Dr. Meire conclude that no new technique is infallible. In making a choice between the different imaging methods, their availability, cost, the type of equipment, the expertise of the medical and technical staff and the inherent capabilities of the systems have to be considered. The most important factor in choosing between the imaging techniques is the capability of the system to answer the specific question required for the management of the patient. The use and limitation of the different methods is determined by their properties. Ultrasound is limited by air and bone and CT employs ionizing radiation, therefore ultrasound is the method of choice in obstetrics and CT for the brain, lungs and bone. Ultrasound is preferred for examination of the lumbar aorta and inferior vena cava. Ultrasound is also used extensively in cardiac diagnosis where CT has little to offer. There is considerable overlap in the abdomen in the use of ultrasound and CT. CT produces better anatomical displays but ultrasound is more widely available and cheaper. Ultrasound should be the initial procedure in the liver, pancreas, kidney, bladder and orbits. If the results are inconclusive or unobtainable, CT is indicated. CT is particularly valuable in demonstrating lymph nodes, pancreatic and suprarenal disease. CT is more valuable for radiotherapy planning than ultrasound. Ultrasound is still dependent on operator skill to produce diagnostic information whereas CT is more objective and less operator dependent. In addition CT is considerably more expensive than ultrasound. Few would disagree with these conclusions but most will be disappointed that Dr. Kreel and Dr. Meire did not include isotope imaging when presenting their conclusions.

This book, like the subjects with which it deals, has its evident limitations. In spite of these it can be recommended very highly to all those interested in medical organ imaging.

F. G. M. ROSS.

1979, *British Journal of Radiology*, 52, 936–941

Desmoid tumour: an angiographic study of five cases

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ABSTRACT

Compared with the frequent reports on the angiographic features of fibrosarcomas only a few similar studies concerning desmoid tumours have been published. Five patients with desmoid tumours and investigated by angiography are reported. The findings were normal in two instances. The forearm tumours of two patients were supplied by unusually large branches of anterior interosseous arteries with normal courses within the tumour. Increased vascularity was seen in these two tumours as well as in a fifth tumour of the buttock. These three tumours behaved more aggressively than the two with entirely normal angiographic appearances. On the basis of the literature and the findings in these five cases there might well exist a positive correlation between the degree of agressiveness of a desmoid tumour and its angiographic features as already established in the case of fibrosarcomas.

Desmoid tumours are rare locally invasive fibromatotic tumours occurring in the anterior abdominal wall, in extra-abdominal sites—preferably the shoulder girdle (Cole and Guiss, 1969)—and in the mesentery (Ackerman, 1954). Arising from musculo-aponeurotic structures they have a strong tendency to persistent growth (Stout and Lattes, 1967). The tumours vary greatly in size and have an ill-defined outline as opposed to the apparent encapsulation seen in fibrosarcomas. The long axis of the tumours is usually oriented in the direction of the fibres of the muscle bundle which they occupy and invade. The incidence has been estimated as two patients per 10^6 people per annum (Dahn *et al.*, 1963, Reitamo, 1978). The borderline between a non-metastasizing desmoid tumour and a well-differentiated fibrosarcoma can be ill-defined as a definite answer cannot be provided by histology alone (Stout, 1948). The angiographic features of soft tissue and bone tumours have been the subject of many communications (Strickland, 1959; Lagergren *et al.*, 1960; Hudson *et al.*, 1975).

These reports have mostly dealt with malignant soft tissue tumours and there have only been a few references to these features in desmoid tumours (Tiwisina, 1957; Krieg and Puls, 1972; Levin *et al.*, 1972; Hill *et al.*, 1973; Parisot *et al.*, 1976; Yaghmai, 1977). The paucity of reports on the angiographic features of desmoid tumours would appear to justify the publication of this report.

MATERIALS AND METHODS

The five patients in the following case reports, one abdominal and four extra-abdominal, were examined by plain radiography and angiography. They form a part of an unpublished series of 89 patients with 92 primary desmoid tumours (Reitamo, 1978) collected from three major institutions of pathology in Finland over a period of 20 years. Most of these patients have not been treated at the Helsinki University Central Hospital. The five patients whose case reports are to follow were seen and treated consecutively at the Helsinki University Central Hospital between 1969 and 1978. Histology alone cannot give the final diagnosis of a desmoid tumour in all cases. However, as desmoid tumours do not metastasize despite their frequent local aggressive behaviour the answer may in some cases be provided by a sufficiently long follow-up period free from metastatic disease. The mean duration of follow-up (time from the first operation to the last contact with the patient) in our five cases is 15.2 years with a range from eight years and nine months to 23 years. The following description of the desmoid tumour (Musgrove and McDonald, 1948; Stout and Lattes, 1967; Mackenzie, 1970) presents the criteria used by the present authors as a basis for the histological diagnosis of a desmoid tumour in the reported cases. A true desmoid tumour lacks apparent encapsulation, a feature common to most true fibrosarcomas. Interwoven bundles of spindle cells are always present with a wide range of cellularity from usually more central and inactive almost acellular fibrous tissue to usually more peripheral and active connective tissue resembling a low-grade fibrosarcoma. While there may be variation in size, shape and cell density only normal mitoses and no hyperchromatic or bizarre nuclei are seen. Infiltration of surrounding muscle produces sarcolemmal giant cells differing distinctly from true tumour giant cells (Fig. 1).

CASE REPORTS

Case 1

A 54-year-old woman had a fourth recurrence of a desmoid tumour 10 cm in diameter of the right arm and axilla. The original tumour had been removed 14 years earlier after having attained a diameter of 20 cm. Histology of the tumour and of all four recurrences showed a sparsely cellular desmoid tumour with muscle invasion. Radiographs showed a soft tissue mass in the region of the right arm. The humerus was normal. Axillary angiography (Fig. 2) was normal. Radical removal of the tumour was followed by an

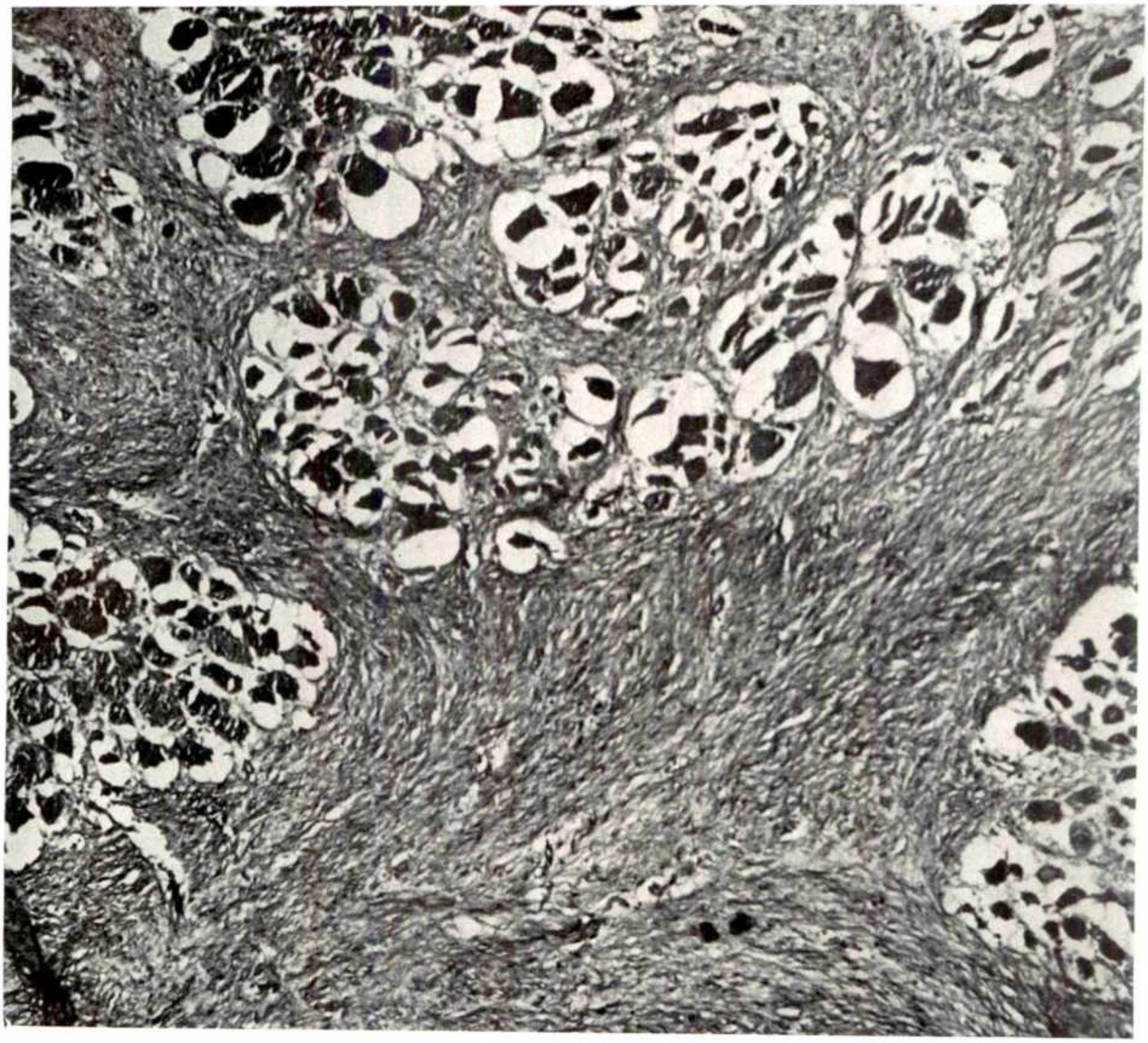

FIG. 1.

Infiltration of gluteus maximus muscle (case 5) by desmoid tumour of left buttock. Note broad bands of hyaline collagen, muscle invasion with formation of sarcolemmal giant cells. Haematoxylin and eosin, ×60.

uneventful recovery. There have not been any further recurrences during a follow-up period of one year and six months.

Case 2

A previously healthy 34-year-old woman noted a 5 cm sized tumour in the left lower quadrant of the abdominal wall four years after Caesarean section. On aortic angiography no dislocation or deformity of the vessels could be seen. Radical removal of a typical desmoid tumour of the external oblique muscle was followed by a tumour-free follow-up period of, so far, seven years and seven months.

Case 3

At the age of six months thickening of her daughter's right forearm was noted by the mother. Radiographs were normal. The tumour had attained a size of 6 cm when radical removal was attempted eight months later with the sacrifice of most of the extensor muscles of the forearm. The histological diagnosis of the tumour and of the later recurrences was aggressive fibromatosis (a more descriptive and possibly more apt pathological term for a variant of the desmoid tumour). The tumour was highly cellular with many normal mitotic figures. Nine months later radiographs of the right forearm (Fig. 3) showed sharply demarcated osteolytic areas. Further radical surgery was undertaken with a sacrifice of the radial nerve and artery and conservation of only a few flexors of the fingers and flexors and extensors of the ulnar side of the wrist. A further recurrence was observed six months later. On brachial angiography (Fig. 4) a large bipartite tumour was seen together with dislocation of the vessels by the tumour. It was supplied and surrounded by sizeable branches of an unusually large anterior interosseous artery. Increased vascularity was seen in the tumour area. There was, however, early visualization of dilated veins, which the examining radiologist interpreted as a sign of a greater malignant potential than had been suspected previously. Despite the known resistance of desmoid tumours to radiotherapy and the risk of malignant transformation (Soule and Scanlon, 1962) 2200 rad from a cobalt teletherapy apparatus were given to the tumour area. Five months later no further growth was discernible. The tumour-free follow-up period is now three years.

Case 4

At the age of three years retardation of growth with distal thickening of their daughter's forearm was observed by her parents. Eleven years later radiographs of the right forearm showed a dense soft tissue mass with bowing-out and erosion of the distal ulnar and radial diaphyses. On brachial angiography (Fig. 5) dislocation of both the ulnar and radial arteries was apparent. The sharply outlined tumour was supplied and surrounded by prominent branches of a large anterior interosseous artery. Increased vascularity and small staining areas were seen in the tumour area. The tumour was excised together with parts of the radius and ulna. Histology showed a markedly cellular and vascular desmoid tumour. There was a recurrence of the tumour four years later. Radiographs showed a defect in the radius. On brachial angiography (Fig. 6) the tumour was seen to be supplied by unusually large branches of the anterior interosseous artery. The calibre of the vessels was normal. The tumour was resected together with a part of the distal ulna. A further recurrence was detected one year later. Brachial angiography (Fig. 7) showed a small soft tissue tumour with normal vascularity. Further radical surgery would necessitate amputation and has as yet not been decided upon.

Case 5

A 46-year-old woman had a tenth operation for a recurrent desmoid tumour of the left buttock. The original tumour measuring 5 cm in diameter had been removed 12 years and nine months prior to the present admission. The histology of the previously removed tumours and that of the present one shows a sparsely cellular tumour with whorled bundles of collagen and muscle invasion with formation of sarcolemmal giant cells. On angiography of the common iliac artery (Fig. 8) the tumour was seen to be supplied by branches of the inferior gluteal artery with distal occlusion of the main stem of the artery due to prior surgery. The tumour was hypervascular and showed faint irregular staining in the capillary phase. These changes were definitely accentuated but no additional features could be observed after an intra-arterial injection of tolazoline (Priscol ® CIBA-GEIGY SA, Zyma SA, Nyon, Switzerland). At operation a tumour 3.5 × 7 cm in size and closely adherent to the left sciatic nerve was removed. Five months later the patient was moving about freely with the aid of a walking stick.

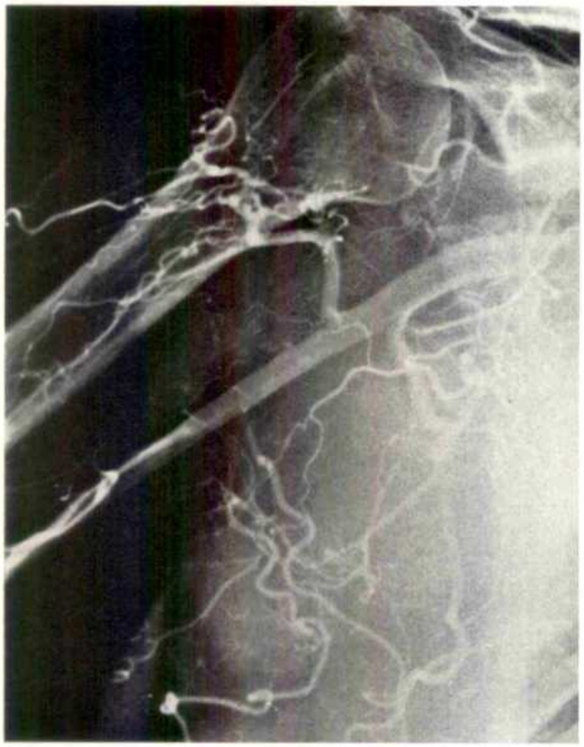

FIG. 2.

Axillary angiogram showing normal axillary artery and branches.

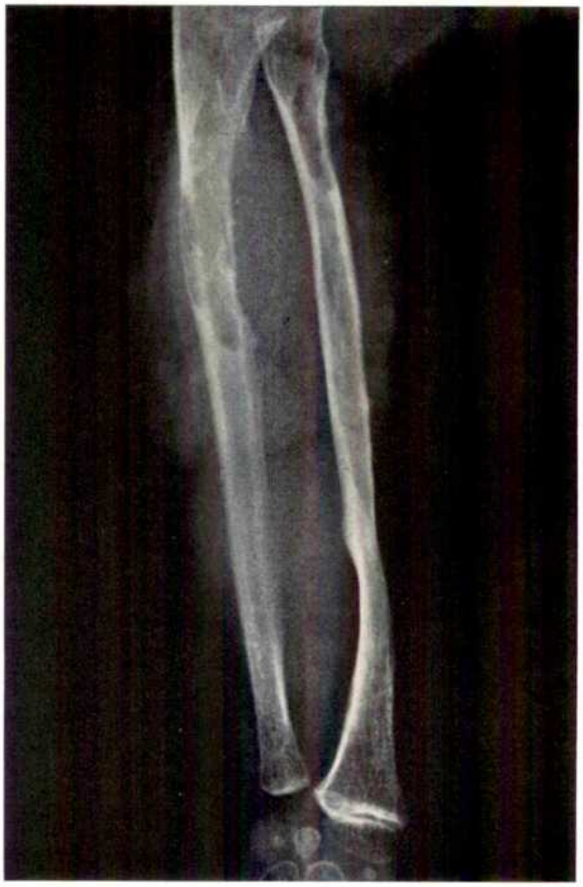

FIG. 3.

Radiograph of forearm with large soft tissue tumour causing sharply outlined erosions with sclerotic margins of proximal ulnar diaphysis.

DISCUSSION

The borderline between a non-metastasizing desmoid tumour (fibromatosis) and a well-differentiated fibrosarcoma capable of dissemination cannot be determined with certainty by histopathology alone (Stout, 1948). There are cases where a final answer will only be provided by the eventual appearance or non-appearance of metastases. There are not infrequent communications on the angiographic features of fibromatous tumours in the case of fibrosarcomas (Strickland, 1959; Levin *et al.*, 1972; Hudson *et al.*, 1975; Ekelund *et al.*, 1977; Yaghmai, 1977). Pathological findings have almost invariably been reported in this context. Neovascularity with non-homogenous staining during the capillary phase and arteriovenous shunting or else hypervascularity, yet with the majority of the vessels involved showing gradual diminution in calibre with staining during the capillary phase, but without arterio-venous shunting, have been reported (Levin *et al.*, 1972; Ney *et al.*, 1972; Ekelund and Lunderquist, 1974; Ekelund *et al.*, 1977; Yaghmai, 1977).

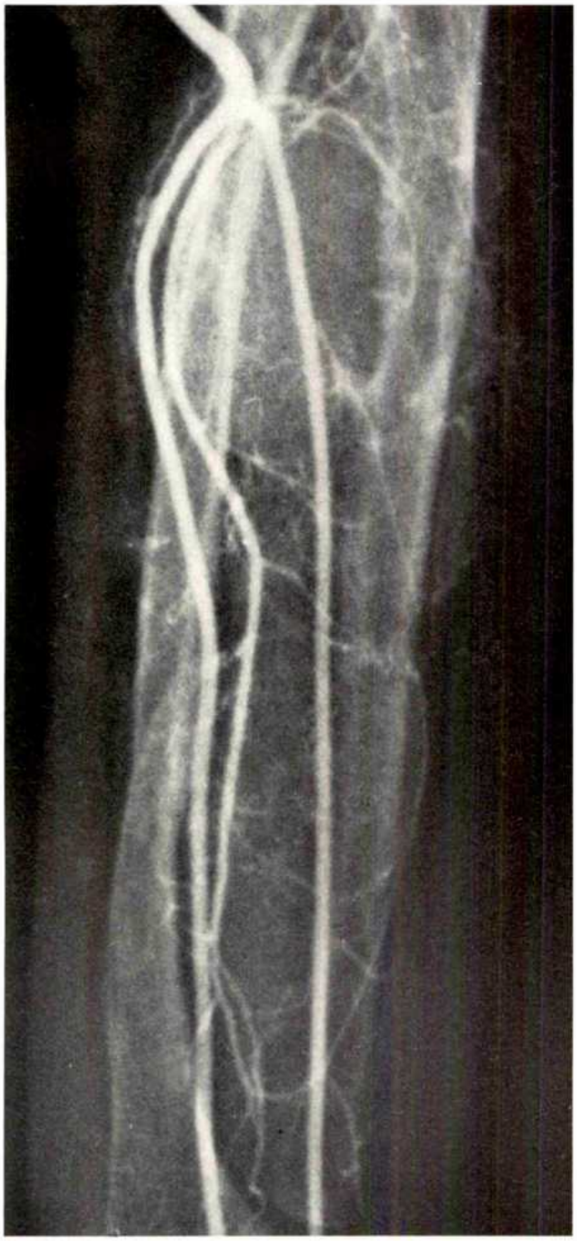

FIG. 4.

Brachial angiogram showing bipartite soft tissue tumour with increased vascularity and causing radial and ulnar deformity. The tumour is surrounded and supplied by unusually large branches of a large anterior interosseous artery.

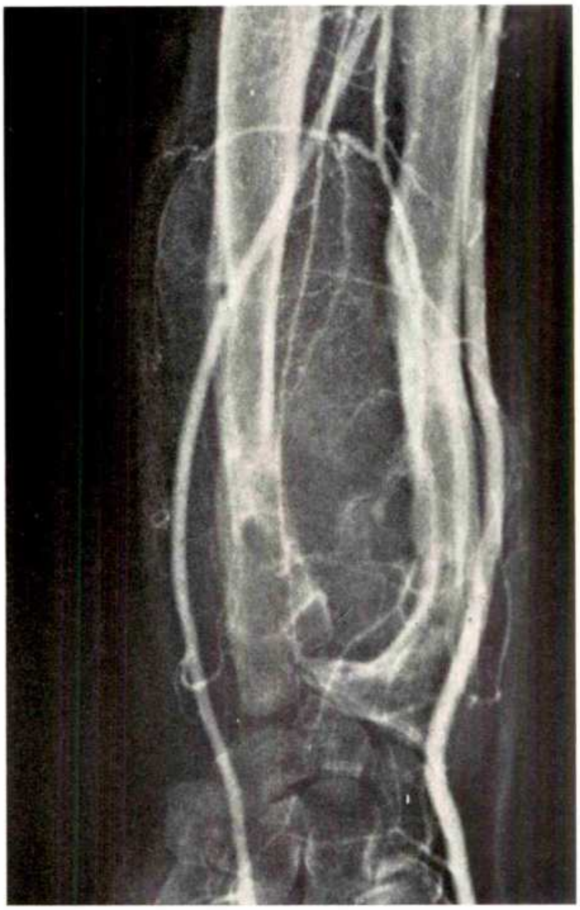

FIG. 5.

Dislocation of radial and ulnar arteries by the tumour. The tumour is circumvented and supplied by large branches of the anterior interosseous artery. There is increased vascularity and faint irregular accumulation of contrast medium in the tumour area.

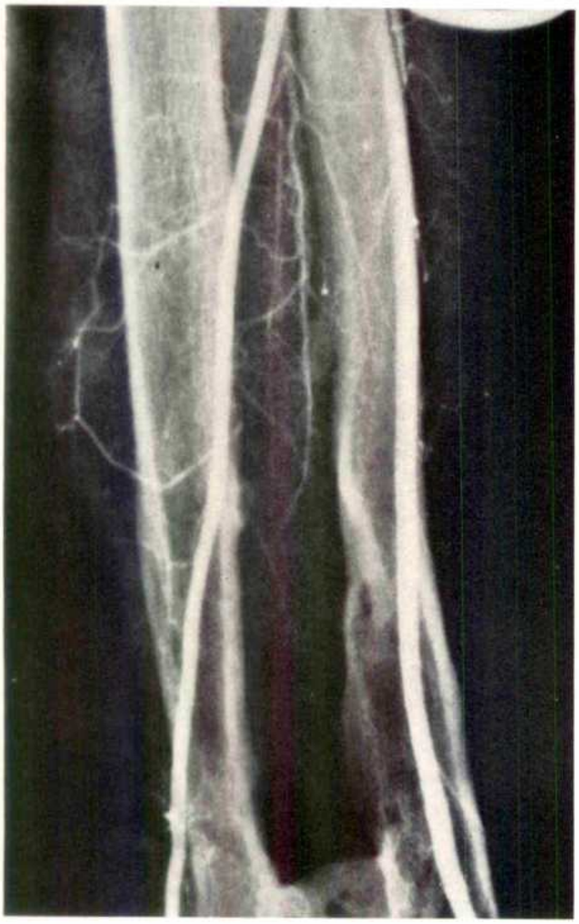

FIG. 6.

Brachial angiogram. Tumour being supplied by the anterior interosseous artery. The branches within the tumour are normal.

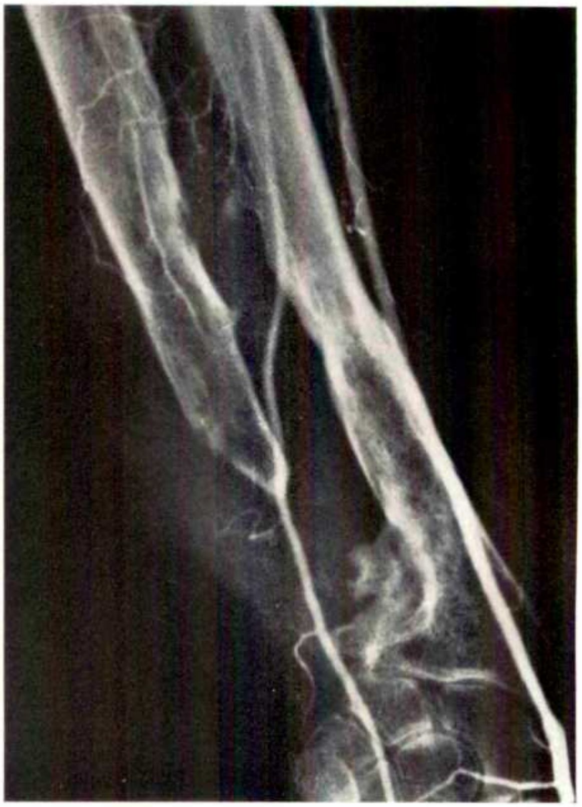

FIG. 7.

Brachial angiogram. Normal vessels are seen entering the tumour.

The angiographic features of desmoid tumours have only rarely been discussed in the literature (Tiwisina, 1957; Krieg and Puls, 1972; Levin *et al.*, 1972; Parisot *et al.*, 1976; Yaghmai, 1977). Yaghmai's series (1977) included only one desmoid among 38 fibromatous tumours. In that particular case the tumour had caused pressure erosion with sclerotic margins of both the radius and the ulna, a feature common both to slowly growing malignant and benign tumours (Cavanagh, 1973), yet angiography was normal. According to Yaghmai the only positive radiological changes in cases of benign fibromatous tumours such as the desmoid consist of dislocation of vessels by the tumour mass. On the other hand, the angiographic features described by Levin *et al.* (1972) in two cases and Hill *et al.* (1973) in one case of desmoid tumour were increased vascularity, staining during the capillary phase and arterio-venous shunting, but no neovascularity. These are features seen in malignancies and in inflammatory tumours, but rarely in benign tumours (Levin *et al.*, 1972; Parisot *et al.*, 1976). Krieg and Puls (1972) reported on a desmoid tumour, which on angiography showed neovascularity, tumour staining during the capillary phase and arterio-venous shunting, i.e. according to present views all features of malignancy (Levin *et al.*, 1972).

In the present study, angiography in two desmoid tumours was normal. The two tumours located in the right forearm were supplied by unusually large branches of prominent anterior interosseous arteries. Both tumours caused pressure erosion of neighbouring bones. The fifth tumour—of the left buttock—was supplied by branches of the inferior gluteal artery. Increased vascularity in the tumour area was seen in all these three cases. The behaviour of the tumours in these cases was more aggressive than

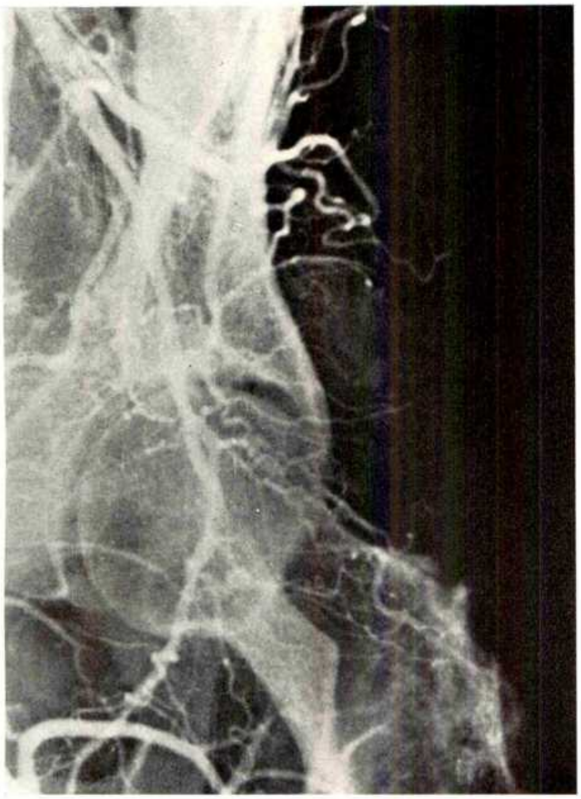

FIG. 8.

Common iliac angiogram. The hypervascular tumour is supplied by branches of the inferior gluteal artery and shows faint irregular staining in the capillary phase. The lower border of the tumour is seen only faintly.

that in the first two cases. Small staining areas with early venous visualization were seen in one of the two tumours of the forearm.

A close correlation has been shown to exist in the case of fibrosarcomas between the angiographic picture and the grade of malignancy. A low-grade tumour is poorly vascularized and conversely a high-grade tumour is highly vascularized (Lagergren *et al.*, 1960). On the basis of the literature and the findings of the present study there might well exist a similar association of increased vascularity and increasing aggressiveness with an appearance of neovascularity in the case of desmoid tumours also. A more definite statement cannot be made on the basis of this small series.

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Intravenous urography in neonates and infants. What dose of contrast should be used?

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Abstract

The dose of contrast to be used for IV urography in neonates and infants is discussed. Toxic levels are only just above the currently accepted doses of 2–4.4 ml contrast medium per kg bodyweight. The dangers of expressing the dose of contrast medium as a volume of contrast related to the patient's age are discussed. A case is presented who had a severe reaction following an acceptable dose expressed as volume for age, but probably excessive when expressed as ml per kg bodyweight.

It is concluded that for IV urography in neonates and infants the dose of contrast must be related to weight of patient and not its age; no dehydration should be used; and the injection should be slow, taking about three minutes.

"The safety of tri-iodenated agents, even with seemingly high doses, is striking" (Baker and Berdon, 1972). "Recommended doses should not be exceeded because they are only slightly below the levels in which toxic effects can be expected" (Miller and Stukas, 1977).

Faced with these apparently contradictory statements, what is the dose of contrast medium that should be used for intravenous urography in neonates (*i.e.* under one month of age) and infants (one month to one year of age)?

Discussion

Dose

Table I shows the dose of contrast,† for intravenous urography, recommended by a number of authorities. Many suggest a dose in the range 2.0–4.4 ml per kg bodyweight. Franken (1977) and Ansell (1976) warn that these doses are just below toxic levels. Although reactions are said to be much less common in infants than in adults and older children (Dunbar and Nogrady, 1972) one should remember Ansell's warning (Ansell, 1970) against the complacent popular belief that "modern contrast media are non-toxic".

Many of the recommended doses in Table I are expressed as a volume of contrast related to the age of the patient. This includes the excellent review article on urography by Saxton (1969) and the manufacturers' recommendation (May & Baker Ltd., 1971; 1978). In their authoritative paediatric textbook Forfar and Arneill (1978) also use a volume for age dose for infants over three months of age. A survey of 72 hospitals for the Society of Paediatric Radiology in 1972 concluded that "most centres use

TABLE I

Dose of contrast medium for intravenous urography (unless otherwise stated the contrast is Conray 280, Hypaque 45% or similar contrast with iodine concentration of 270–280 mg per ml)

Saxton (1969)	neonates	20 ml
	infants and children	20–40 ml Conray 420
Ansell (1970)	infants	2.2–4.4 ml/kg
May & Baker Ltd. (1971) p. 30	neonates	20 ml
	infants and children	20–40 ml Conray 420
p. 59	under 6 months	10 ml
	6 months to 2 years	20 ml
Saxton and Strickland (1972)	neonates and infants	3 ml/kg
	children	20–40 ml Conray 420
Dunbar and Nogrady (1972)	under 1 year	3 ml/kg
Cockburn and Drillien (1975)	neonates	3 ml/kg (occasionally up to 5 ml/kg)
Poznanski (1976)	infants and children	2–4 ml/kg
Franken (1977)	under 1 month	3–4.4 ml/kg
	over 1 month	1.5–2 ml/kg
Gordon and Ross (1977)	under 8 kg	2.5 ml/kg
	8–30 kg	20 ml
Forfar and Arneill (1978)	0–3 months	3 ml/kg
	3 months–8 years	20 ml
	8–12 years	20–40 ml
May & Baker Ltd. (1978)	under 6 months	10 ml
	6 months–2 years	20 ml

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†Iodine concentration 270–280 mg per ml, *e.g.* Hypaque, 45%, Conray 280.

a dose of approximately 10 ml contrast for a neonate and 12–15 ml for age one to six months" (Baker & Bardon, 1972). In this survey 39 hospitals calculated dose as volume contrast related to age of patient. This practice is considered to be most dangerous and should be strongly condemned. A newborn infant can weigh under 1 kg or over 5 kg and it is unwise to use the same dose of contrast for a 1 kg baby as for one five times its weight.

It is our belief, therefore, that contrast dose should only be expressed as ml contrast per kg bodyweight.

Toxicity

The overall death rate from contrast urography is about one death per 40000 investigations (Ansell, 1975). In adults, deaths may be due to allergic reactions. Gooding *et al.* (1975) reported five severe reactions in 12500 urograms in children. The ages were 3.5 to 12 years. In four cases "allergy" was important.

In neonates and infants severe reactions are mainly due to the osmotic effects of the contrast (Miller and Skucas, 1977; Friesinger *et al.*, 1965; Ansell, 1976). It is thus dose related. Conray 280 has an osmolarity of 1480 mosmols/litre (Miller and Stucas, 1977). This compares with a serum osmolarity of 280–300 mosmol/litre (Cockburn and Drillien, 1975). An injection of 4 ml per kg of contrast is almost 10% of the baby's blood volume. It has been shown to increase the osmolarity of the serum in infants by 6–39 mosmols/litre (mean 15) (Standen *et al.*, 1961). The rapid increase in serum osmolarity draws fluid from the tissues into vessels, with a risk of cellular dehydration and heart failure with pulmonary oedema (Ansell, 1970). Recent reports of deaths or severe reactions to contrast in infants all indicated overdosage. With the three deaths the doses were as follows:
250 ml Urografin 30%—2.9 kg weight infant (Ansell, 1970); 25 ml Urovision—2.2 kg weight infant (Ansell, 1970); 14 ml Conray 280—1.6 kg weight infant (McClennon *et al.*, 1972). A fourth baby weighing 3.6 kg received 40 ml of urografin 60 (Ansell, 1970). This baby had fits and coma but recovered.

We recently saw a severe reaction in a 2.25 kg baby inadvertently given 15 ml of conray 280. This dose is well within the dose range recommended by Saxton (1969) and is equivalent to about 6.5 ml per kg. This infant was found apnoeic and cyanosed with marked bradycardia, 50 minutes after the end of injection. It had convulsions but recovered after several days of artificial ventilation. CAT scan four days after the initial collapse revealed widespread patchy areas of cerebral oedema.

Rate of injection

Poznanski feels that a rapid injection of contrast is desirable to give a better nephrogram (Poznanski, 1976). As toxicity is due to osmotic changes and as these changes occur very rapidly (Standen *et al.*, 1961) we agree with other workers (Saxton, 1969; Miller and Skucas, 1977; Poznanski, 1976; Cockburn and Drillien, 1975) that a slow injection over about three minutes is desirable.

Dehydration

As toxicity of contrast in the very young is due to osmotic changes, dehydration is dangerous (Cockburn and Drillien, 1975; Miller and Stucas, 1977; Saxton, 1969; Standen *et al.*, 1961). We feel that the examination should be done about two hours after a feed and disagree with Forfar and Arneill (1978) who state that "fluid deprivation overnight is safe but not necessary with high doses—omit the feed before the examination".

Age of investigation

During the first few days of life the baby's kidney functions poorly. The glomerular filtration rate is low and the kidney cannot cope well with either a fluid or a solute load (Cockburn and Drillien, 1975). It is for this reason, that the dose of contrast per kg bodyweight recommended for urography is usually higher than at any other time during life. These relatively high doses (up to 4.4 ml/kg) are needed to get adequate visualization of the kidneys. Unfortunately, it is at this age that the risks of toxicity are greatest and maximal changes in serum osmolarity occur after IV contrast injection (Standen *et al.*, 1961). For this reason, unless clinically urgent, studies with intravenous contrast should be delayed until after the first few weeks of life.

CONCLUSION

Severe toxic reactions to IV contrast injection occurring in neonates and infants are considered to be due to the osmotic effects of the contrast medium. An acceptable dose would be in the range of 2–4.4 ml contrast (approximately 270–280 mg I per ml) per kg bodyweight. These doses are close to toxic levels and should not be exceeded. The common practice of stating a dose related to the patient's age is to be deplored. In all cases the dose must be related to the bodyweight and not the age of the patient.

The patient should not be dehydrated. The injection must be slow, approximately three minutes.

Where urgent urograms are required in the first few days of life, especially in pre-term infants, strong consideration should be given to the use of a non-ionic contrast such as amipaque (metrizamide). In a concentration of 170 mg I_2 per ml it is isotonic with blood. This compares with Conray 280 which has an osmolarity of five times that of serum.

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Book reviews

Xeroradiography of the Lung and Mediastinum. By G. Tricomi, L. Saracca, M. L. Palozzi and P. Falappa, pp.223, 1979 (Excerpta Medica, Amsterdam, Oxford), 70,000L. ISBN 90-219-0401-2

This beautifully produced book, priced at about £40, has the apparent objective (stated in the introduction) of acting as "a spur to a discussion about the new things that this technique prefigures . . . in chest diagnostics". I doubt if this objective will be achieved. The book deserves criticism for many reasons. The presentation is confusing, the quaint English translation (printed alongside the Italian) is difficult to follow and occasionally incomprehensible. Much of the text describes straightforward pathology, and the clinical relevance of the various investigations presented is largely ignored. No formal comparative studies between xeroradiography, xerotomography, and conventional film techniques appear to have been carried out. Indeed, xerotomograms of a lesion are often illustrated alongside a plain film of the same lesion. When conventional tomograms are illustrated, the technical quality leaves much to be desired. Both positive and negative mode xerograms are illustrated without comment on their relative merits. The orientation of the illustrations varies from page to page and even some of the film illustrations are presented as positives. The text is often remote from the illustrations.

However, despite these many difficulties, the qualities of edge enhancement and latitude inherent in the xerox image often produce vivid demonstrations of thoracic structures. It may be as an atlas of chest anatomy and pathology that the book has some merit, but I doubt if many Radiology Departments will wish to purchase it for that reason alone. As a contribution to the difficult process of evaluating the role of different imaging methods in radiology, the book cannot be recommended.

J. SPENCER.

The Radiology of Acute Cervical Spine Trauma. By John H. Harris, pp. xiii+116, illus. 1978 (Williams & Wilkins, Baltimore) $20.95/£13·50.
ISBN 0-683-03927-X.

Those who have read Dr. Harris's excellent article in Seminars in Roentgenology in January 1978 will welcome this text book which enables the author to expand and develop the themes he introduced in that article. In writing another book on neck injuries he is following in distinguished footsteps. Penning's classic monograph discusses the theory and mechanisms of trauma in greater detail: more recently Kattan edited an excellent and profusely illustrated text book on the same subject in 300 pages. Dr. Harris somehow contrives to squeeze "what every radiologist should know about cervical injuries" into 100 pages with 86 illustrations. This is achieved by a beautifully concise prose style and illustrations which, because of their quality, can say in one picture what other authors may require to illustrate two or three times.

Like most people interested in the neck, Dr. Harris has strong personal views about the mechanism of certain injuries, notably the distinction between flexion and compression ("burst") fracture. He takes to task certain authors for making their classification either too complex or alternatively too simple thereby excluding some types of injury. He admits that distinction may not be possible on radiographic appearances alone but makes the important point that flexion (tear-drop) fracture is unstable and frequently reveals itself clinically by neurological complications.

The author's clarity of thought and expression result in a text that has no ambiguities either of description or argument which means that this book is an ideal introduction for the newcomer to this field. At the same time, there is an ample list of references for those who wish to read more deeply on a given topic. Strongly recommended as a benchbook.

J. T. PATTON.

1979, *British Journal of Radiology*, *52*, 945–948 DECEMBER 1979

The accuracy of ultrasound in the detection of cirrhosis of the liver

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ABSTRACT

The association of high amplitude echoes returned from the liver and cirrhosis is well recognized. There have been no reports in the literature as to the overall incidence of this finding in the clinical situation. We report our experience in a series of 67 patients with proven cirrhosis who had liver biopsy and an ultrasound examination within three months of one another. In 43 patients cirrhosis was suggested by recognition of a bright liver echo pattern. In 23 patients the liver echo pattern was normal, although additional relevant information was shown in half of this group. The detailed pathology has been analysed in an attempt to account for the false negative examinations, revealing a strong trend for cases of micronodular cirrhosis to give positive ultrasound examinations and macronodular cirrhosis negative examinations.

It has been recognized for some years that in cirrhosis high amplitude echoes may be returned from the liver giving rise to a bright liver echo pattern. It has been suggested that the echoes from an organ arise predominantly from the fibrous skeleton (Fields and Dunn, 1973). Since the pathology of cirrhosis is the progressive disruption of the liver architecture with replacement by fibrous tissue, it might be expected that cirrhotic livers with increased fibrous tissue content would generate high amplitude echoes. A number of authors have confirmed that this is true (Mountford and Wells, 1972; Taylor, *et al.*, 1976; Sanders and Sanders, 1977).

We have recently reported our experience on the significance of recognition of a typical bright liver echo pattern at ultrasound examination (Joseph *et al.*, 1979). Several facts emerged from this study. Firstly the ultrasound finding of a bright liver echo pattern was highly significant, always corresponding to one of a small group of liver pathologies. Secondly the majority of patients in this study were found to have cirrhosis. And finally we became aware whilst carrying out this study that several patients with cirrhosis had normal liver ultrasound examinations. It was therefore apparent that ultrasound would not be a reliable screening procedure for detection of cirrhosis and that the histopathological reason for a bright liver echo pattern was more complex than simply the presence of fibrous tissue within the liver.

The present study has been undertaken to establish the reliability with which ultrasound will detect cirrhosis. We are unaware of any other such studies reported in the English literature.

SUBJECTS AND METHODS

The full biopsy reports of all patients who had cirrhosis of the liver diagnosed in the last two years were obtained. Patients were included in the study if an ultrasound examination and a liver biopsy had been carried out within three months of one another. In the majority of patients the ultrasound examination and the liver biopsy were separated by no more than a few days to a few weeks. This yielded a total of 69 patients. Two of these were excluded, one because the ultrasound was recorded as a technical failure and the other a neonate with secondary biliary cirrhosis and biliary atresia. This left a total of 67 patients for full analysis.

All the ultrasound studies were carried out on a commercially available grey scale machine using either a 2.25 MHz or 3.5 MHz internally focused transducer. The assessment of the liver parenchymal echo pattern was made on longitudinal scans of the liver obtained by the standard single sweep technique. The bright liver echo pattern is recognized at standard instrument settings, although higher gain settings may be required for optimal results.

RESULTS

The first step was to divide the 67 patients in this series into groups according to the type of echo pattern identified at the ultrasound examination. These results are recorded in Table I. There are two main groups; the single patient in group three will be briefly mentioned later. In the first group of 43

TABLE I

ULTRASOUND IN THE DIAGNOSIS OF CIRRHOSIS

1. Bright echo pattern	43 patients (65%)
2. Normal echo pattern	23 patients (35%)
3. Other echo pattern	1 patient —
Total 67 patients	

patients a diagnosis of cirrhosis was strongly suggested by the recognition at ultrasound examination of a bright liver echo pattern. This confirms that ultrasound is not a reliable screening procedure for the detection of cirrhosis, but that two out of three cases can be recognized. A careful analysis of the full pathology reports had been made in an attempt to define any factors which may account for the production of a bright liver echo pattern. Because the numbers are small and the pathology reports are difficult to analyse in a precise way, the incidence of various pathological findings are quoted in approximate percentages. About 50% of the patients had micronodular cirrhosis, the remainder a mixed pattern cirrhosis—macronodular cirrhosis or an unspecified type. 30% of patients in this group showed evidence of fatty infiltration, 20% of patients evidence of hepatitis and 15% evidence of piecemeal necrosis. More than one of these features may be recorded in the same patient. The observation of a bright liver echo pattern remains a subjective assessment. Its validity rests on the fact that in a consecutive series of patients with this finding, one of a well defined group of pathological entities has been shown at biopsy in all cases (Joseph *et al.*, 1979). Our original series consisted of 45 patients but this has now been extended to include 88 patients at the present time. There have been no false positive ultrasound results to date. On a subjective basis it is possible to subdivide the bright liver echo pattern into three types:

1. marked fine bright pattern;
2. marked coarse bright pattern;
3. moderate bright pattern.

Examples of these patterns are illustrated in Figs. 1, 2 and 3. Figure 4 shows a normal liver for comparison. With all these three types it is also possible to note the presence of significant distal attenuation of the sound beam. This is a particularly subjective feature to assess, heavily dependent on machine control settings, and so for this reason we have not considered it further.

It is clear that the pathological findings vary considerably from patient to patient both in detail and in overall severity. We have been unable to show any correlation between a specific pathological finding and the ultrasound echo pattern to suggest a tissue specificity for the findings in this group. In this respect our experience differs from that of other workers who have taken the two ends of the spectrum, the coarse bright liver with marked distal attenuation and the fine bright liver with no increase in attenuation, as being characteristic of cirrhosis and fatty infiltration respectively (Taylor, 1978). In our present study and a previously reported study (Joseph *et al.*, 1979) we have found the overlap has been too great to be of real value.

In the second group of 23 patients with cirrhosis, the liver echo pattern was considered within normal limits. In spite of this, however, abnormalities were reported in just over half the patients in this group. The most common abnormalities recorded were

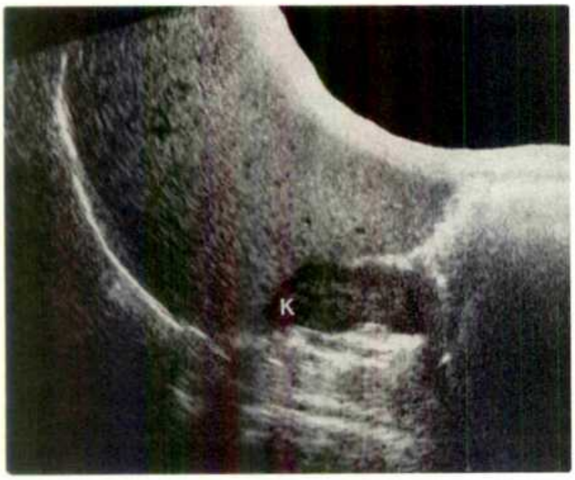

FIG. 1.

Marked fine bright pattern. A longitudinal scan through the right lobe of the liver showing the right kidney (K). Note the high overall amplitude of the liver echoes, which are individually small and tightly packed. The liver has a uniform appearance. Portal vein walls cannot be clearly distinguished.

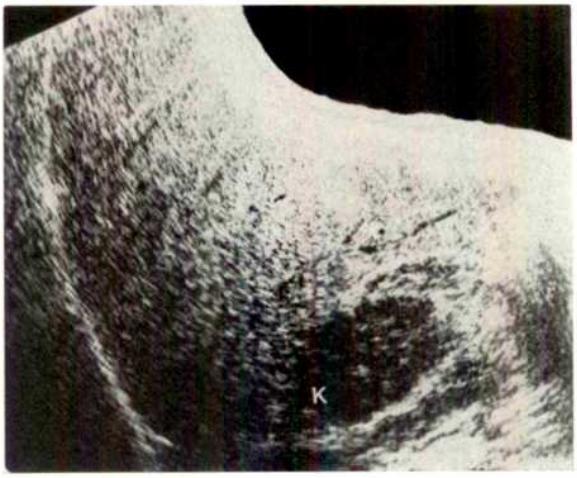

FIG. 2.

Marked coarse bright pattern. A longitudinal scan through the right lobe of the liver showing the right kidney (K). The overall amplitude of the parenchymal echoes is high, but the individual echoes are coarse. There is distal attenuation of the sound beam.

splenomegaly, hepatomegaly, ascites, portal vein enlargement and portal vein fibrosis. In a clinical context these are all findings of relevance in a patient with cirrhosis. As in the first group a careful analysis has been made of the full pathology reports, and the findings presented as approximate percentages of the group. In this group, 66% of the patients had a macronodular cirrhosis, 50% of the patients showing evidence of piecemeal necrosis. Only 15% showed a micronodular cirrhosis and 15% some fatty change. In addition, the two cases of primary biliary cirrhosis in the series were in this group. These findings are compared with the findings in the first group in Table II. Since we have used some approximations, and the individual groups are rather small, firm conclusions cannot be drawn from these figures. However it is of interest to note that there are some major differences. Micronodular cirrhosis and fatty infiltration are more likely to give a bright liver echo pattern, and macronodular cirrhosis and piecemeal necrosis more likely to show a normal liver echo pattern.

TABLE II

COMPARISON OF PATHOLOGICAL FINDINGS

Selected features	Patients with bright pattern exhibiting each feature, % (Group 1—43 patients)	Patients with normal pattern exhibiting each feature, % (Group 2—23 patients)
Micronodular cirrhosis	50	15
Macronodular cirrhosis	10	66
Piecemeal necrosis	15	50
Fatty change	30	15

Finally, the one patient in group 3 had an ultrasound examination which showed numerous varying sized metastases in a very large liver. Ascites was noted. The patient had had a Dukes B carcinoma of the colon resected in 1970. A subsequent biopsy showed changes of fibrosis and cirrhosis.

DISCUSSION

In this series ultrasound was able to suggest the presence of cirrhosis in 65% of patients by recognition of a bright liver echo pattern. We have not been able to show any correlation between the detailed pathology or the severity of change and the ease of detection by ultrasound in this group. Comparison between the two main groups shows that there is a considerable amount of overlap. However a definite trend does become apparent. Micronodular cirrhosis with or without fatty infiltration is more likely to yield a positive ultrasound result. In fact if all the cases of micronodular cirrhosis are considered together ultrasound will be positive in over 80% of cases. Macronodular cirrhosis with or without piecemeal necrosis is most likely to yield a negative result. Again, if these cases are considered as a group ultrasound will be negative in approximately 80% of cases. Whilst this is only a trend, it is a substantial

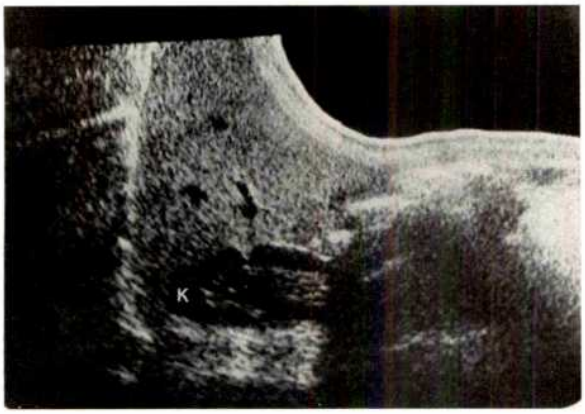

FIG. 3.

Moderate bright pattern. A longitudinal scan through the right lobe of the liver showing the right kidney (K). The moderate overall brightness of the echo pattern is confirmed by the loss of the normal portal vein walls and the relatively black appearance of the kidney.

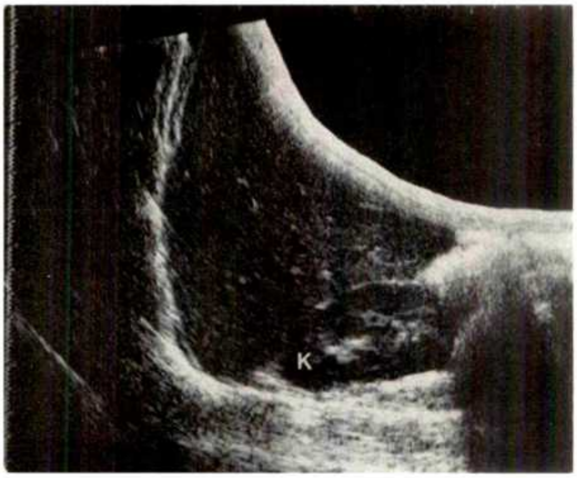

FIG. 4.

Normal. A longitudinal scan through the right lobe of the liver showing the right kidney (K). The liver echo pattern is normal. Compare this with Figs. 1, 2 and 3.

one in this series and may provide a clue to the aetiology of the ultrasound appearances. The precise origin of bright echoes returned from the liver remains unresolved. An increase in the fibrous tissue content of the liver has been shown to be the cause by some workers (Wells *et al.*, 1975). This does not seem surprising since the elastic modulus of collagen fibres is approximately 1000 times greater than that of other soft tissues. This produces large acoustic impedance mismatches and therefore strong echoes at collagen/soft tissue interfaces. However, in a comprehensive study of fatty tissue and tumours Behan and Kazam (1978) have shown that fat is strongly echogenic. In our analysis of the bright liver echo pattern (Joseph *et al.*, 1979) we showed that fatty livers with no evidence of fibrosis and cirrhotic livers with no evidence of significant fatty infiltration may both show similar ultrasound appearances of bright echo patterns. The precise reason why fatty tissue is echogenic is unclear. Experiments have shown that *in vitro* an emulsion of fat and water is highly echogenic (Behan and Kazam, 1978). This is probably because the ultrasonic velocity is reduced by about 10% in fat as compared with other soft tissues; this leads to relatively large acoustic impedance mismatches at soft tissue/fat interfaces. In fatty infiltration of the liver the globular fat cells can be considered as in emulsion within the "water phase" of the surrounding soft tissues. It seems clear that there are two possible causes of brightly reflective echo patterns in the liver, fibrous tissue and fatty tissue. Since hepatic fibrosis and fatty infiltration frequently co-exist it is difficult to study their effects independently or to study how the two aspects interact with one another.

The reliability with which ultrasound will detect the fatty liver with no significant fibrosis is not yet known. However, this study has clearly shown that ultrasound will show a normal echo pattern in the majority of cases of macronodular cirrhosis even in the presence of extensive fibrous tissue. The reason for this remains unresolved at present.

CONCLUSION

We have shown that ultrasound will indicate the presence of cirrhosis in 65% of an unselected series, by the recognition of a characteristic bright liver echo pattern. In cases of micronodular cirrhosis, ultrasound is likely to detect about 80% of patients, and in macronodular cirrhosis only 20% of patients. Where ultrasound produces a bright liver echo pattern we have been unable to correlate variations in this pattern with the detailed pathology. Both fibrous tissue and fatty tissue can give rise to high amplitude echoes and so give a bright liver picture. The reason that this does not occur in all cases of cirrhosis remains unresolved.

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Book review

Real-time Ophthalmic Ultrasonography. By S. N. Hassani and R. L. Bard, pp. xix+214, 1978 (Springer Verlag KG, Berlin), DM.69/$38.00.
ISBN 3-540-90318-6

The book has been produced with a broad readership in mind and has therefore large sections dealing with the basic principles of ultrasound, the anatomy and the ultrasonic anatomy of the orbit. These are useful but unfortunately many of the diagrams are poor and the captions are not always clear. Later in the book the technique of separating captions from the relevant photograph occurs from time to time and is tedious and inconvenient. In parts the text is redundant and rather conversational. Dr. Hassani and his colleague have used the Bronson Contact Real-time Scanner and polaroid film as a recording medium both with their inherent limitations; nevertheless, the full potential of the method is illustrated in the very large range of pathological processes which are described and illustrated. Valuable descriptions of the clinical aspects are given throughout the book and related to the ultrasonic appearances.

Despite the deficiencies I think radiologists and other ultrasonographers who have little experience of ophthalmology will find this book useful from both the ultrasonic and the clinical point of view. There is a glossary of ophthalmological terms and a bibliography of over 200 references.

G. R. SUTHERLAND.

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Ultrasonic diffraction analysis in the investigation of liver disease

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ABSTRACT

An ultrasonic analytical method has been developed which is capable of remote, *in vivo* differentiation between various types of soft tissue on the basis of differences in their gross histological structure. The method is analogous to that employed in X-ray crystallography and is referred to as ultrasonic diffraction analysis. A clinical trial of this method in the investigation of liver disease in 70 patients is reported, in which a total of 416 ultrasonic diffraction patterns associated with various liver conditions have been analysed and related to independent follow-up information. The existance of a malignant condition of the liver has been identified in 95% of the cases involving focal metastatic deposits and in all of the 11 cases studied where the livers had diffuse malignant involvement. Cirrhosis and secondary involvement of the liver due to Hodgkin's disease have also been shown to exhibit specific tissue signatures which enable them to be differentiated from other hepatic disorders.

Although ultrasonic imaging is now firmly established as a technique for the investigation of many problems in oncology (Hill *et al.*, 1978a) there exist some contradictory descriptions of the ultrasonic appearances associated with a number of particular conditions.

The echo patterns caused by primary and metastatic intrahepatic lesions, for example, have received varying descriptions from different authors. Taylor *et al.* (1973) described the typical appearance as areas of low-level echoes within the normal liver. Other manifestations of liver metastases were found to be uncommon. Conversely, McArdle (1976) found, from a study of 21 patients, that the most frequent patterns for liver metastases consisted of echogenic nodules and anechoic regions within an echogenic parenchyma. McArdle's statement that "the appearance of metastases within the liver vary and no single appearance is characteristic of all metastases" is indicative of the need for a more quantitative approach to tissue characterization. It must also be emphasized that many metastases may not be distinguished from normal tissue on the basis of echo amplitude alone. An interesting premise, however, is that the reflectivity of metastases may be dependent upon the site of the primary neoplasm.

Although the ultrasonic appearances of focal liver metastases are inconclusive, the determination of their existence is usually reliable provided they are larger than about 2 cm diameter. The major problems occur when attempting to diagnose diffuse infiltrations of the liver. With the possible exception of cirrhosis, which is usually recognized by the generally increased level of echoes within the liver parenchyma, the majority of diffuse disorders are only registered (if at all) as a slight change in the general pattern of parenchymal echoes, as for example in the case of fatty infiltration.

It seems that clinical diagnosis using ultrasound is still very much dependent upon the diagnostician and his particular machine, and is thus very subjective in its approach. Although much useful and accurate diagnosis is being achieved, a more desirable method would be one in which a quantitative relationship between the scattered echoes and the structural composition of the interrogated tissues was obtained. This, of course, demands that any pathological abnormality in a tissue must be related to a structural variance from normal: a fairly realistic premise.

It is generally accepted that the echoes returning to the transducer are due to a scattering process occurring within the tissue (Hill, 1978) and it seems reasonable, therefore, to suppose that the backscattered echoes are dependent upon the arrangement of scatterers within that tissue (Nicholas, 1978a). It has previously been demonstrated (Nicholas and Hill, 1975a, b) that human soft tissues can be characterized by utilising a diffraction phenomenon analogous to the Bragg diffraction of X rays by crystalline structures. These results showed that, in a pulse echo system, if a sample of tissue is rotated relative to the beam axis, the amplitude of the frequency-filtered backscattered signal, from a small tissue volume located on the axis of rotation, varies with angle. Moreover, the diffraction patterns (relationships of echo amplitude to orientation angle) thus formed were found to characterize differing tissue types and pathologies (Nicholas, 1976, 1978b). It has been postulated by Hill *et al.* (1978b) that the tissues examined comprise a semi-regular array of scatterers over the small volume being interrogated, and that the diffraction patterns result from constructive and destructive interference of the back-scattered signal from each scatterer. Since many diseases only result in a subtle change in the structural composition of a tissue it seems likely that any technique which is capable of monitoring such changes could have immense diagnostic implications.

METHODS

The equipment and methods used for laboratory implementation of this technique have been described previously (Nicholas and Hill, 1975a, b), and a prototype equipment designed for clinical application, with the examination performed in a manner similar to that used for conventional B-scanning, has been described by Huggins and Phelps (1977). The results reported here have been obtained using the latter equipment modified to be capable of providing a conventional B-scan image in addition to the diffraction information.

The principal of this arrangement is indicated in Fig. 1, further details of the geometry and electronics being given in earlier papers. The mechanical scanning facilities consist of a pantograph and a linear B-scan arrangement, either of which can be clamped whilst the other is in operation. With the pantograph movement clamped to leave the transducer in a vertical orientation an exploratory linear B-scan can be performed. Having located a tissue region of interest the linear movement is clamped and the pantograph adjusted so that the transducer moves in such a way that the region of interest is at the isocentre of the beam axis. The imaging facility is now restricted to that of an "isocentric B-scan" but, by means of appropriate electronics, previously described, a diffraction pattern corresponding to the tissue region of interest is simultaneously recorded. In our present arrangement the diffraction information is accumulated on-line in a PDP/8e minicomputer for subsequent analysis.

Pulse echo diffraction

The *in vitro* diffraction experiments exploited the fact that, by electronically time-gating the back-scattered echoes from a tissue organ, a specific volume of tissue, determined by the gate length and transducer beam-width, could be investigated independently of the rest of the organ. Although the *in vivo* requirements are identical, a complicating factor is the duration of the investigating pulse. Fourier analysis shows that the shorter the pulse duration the broader is its corresponding frequency spectrum. This leads to an immediate conflict in requirements. For scanning purposes the axial resolution necessary for adequate imaging demands as short a pulse as is possible so as to separate, in time, the echoes returning from closely spaced scatterers. The relationship of diffractive phenomena to structural arrangement, however, is normally considered to be associated with continuous waves. This apparent disparity can be overcome by frequency filtering the time-gated portion of the backscattered echo train. Derivation of the frequency spectrum of a gated pulse results, analytically, in a convolution of the spectrum of the pulse with that of the time gate. Hence, for example, any single component of the frequency spectrum of a signal selected by a 10 μs time gate will have an associated bandwidth of 100 kHz. By recording only the amplitude of a specific frequency component the investigation is limited to a single frequency (a continuous wave) convoluted with a 100 kHz bandwidth (the time gate). The overall effect is that the interrogating pulse is essentially a time-gated continuous wave. This technique allows a great flexibility in the control of the investigating parameters and in particular makes possible the simultaneous use of a short pulse for conventional B-scan imaging and the continuous-wave analysis of backscattering for quantitative assessment. A block diagram of the electronics is displayed in Fig. 2.

The three parameters determining the outcome of the diffraction procedure are the ultrasound frequency, transducer beam-width and time-gate duration. Of these the latter two determine the tissue volume under investigation. Although the absolute values for these parameters can be fairly arbitrary, certain limits must be observed. The volume of tissue investigated must be small enough to encompass a region of tissue which exhibits short-range local order: typically a few liver lobules (of the order of 5–10 mm) and yet larger than the wavelength. At the same time, the transducer characteristics must be commensurate with abdominal B-scanning requirements. For all the results presented here the transducer used was weakly focussed, with a 6 dB beam width of 5 mm between 4 and 9 cm from the transducer face (as measured in water), and had a nominal working frequency of 2.5 MHz. The time-gate duration was kept constant at 10 μs, allowing approximately 7.5 mm depth of tissue to be investigated.

Data analysis

Although the diffraction patterns collected by this machine can be assessed visually, the main objective is a quantitative characterization of tissue pathology. This should eliminate any operator bias and allow an objective evaluation on a rigorous scientific basis.

Our early observations indicated that the diffraction patterns resulting from different histological structures differ particularly in the rate of angular variation of echo amplitude (see, for example, Fig. 8) and this suggests the application of spectrum analysis techniques for objective characterization (Nicholas and Hill, 1975a). The present approach involves the Fourier transformation of the angular diffraction patterns into the angular frequency domain. This results in an amplitude angular frequency spectrum,

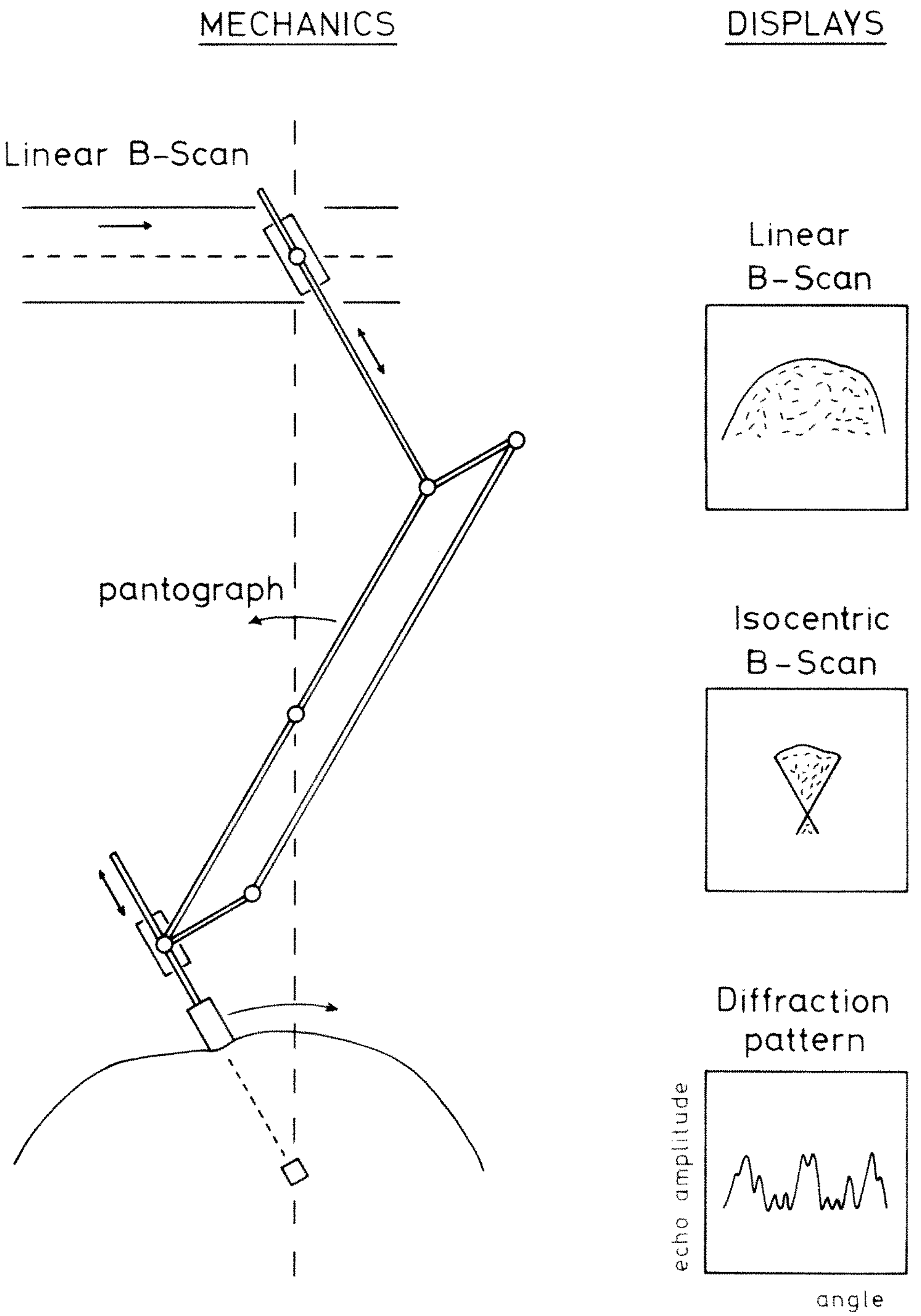

FIG. 1.
Mechanical arrangement of scanning arm and related imaging and analytical modes.

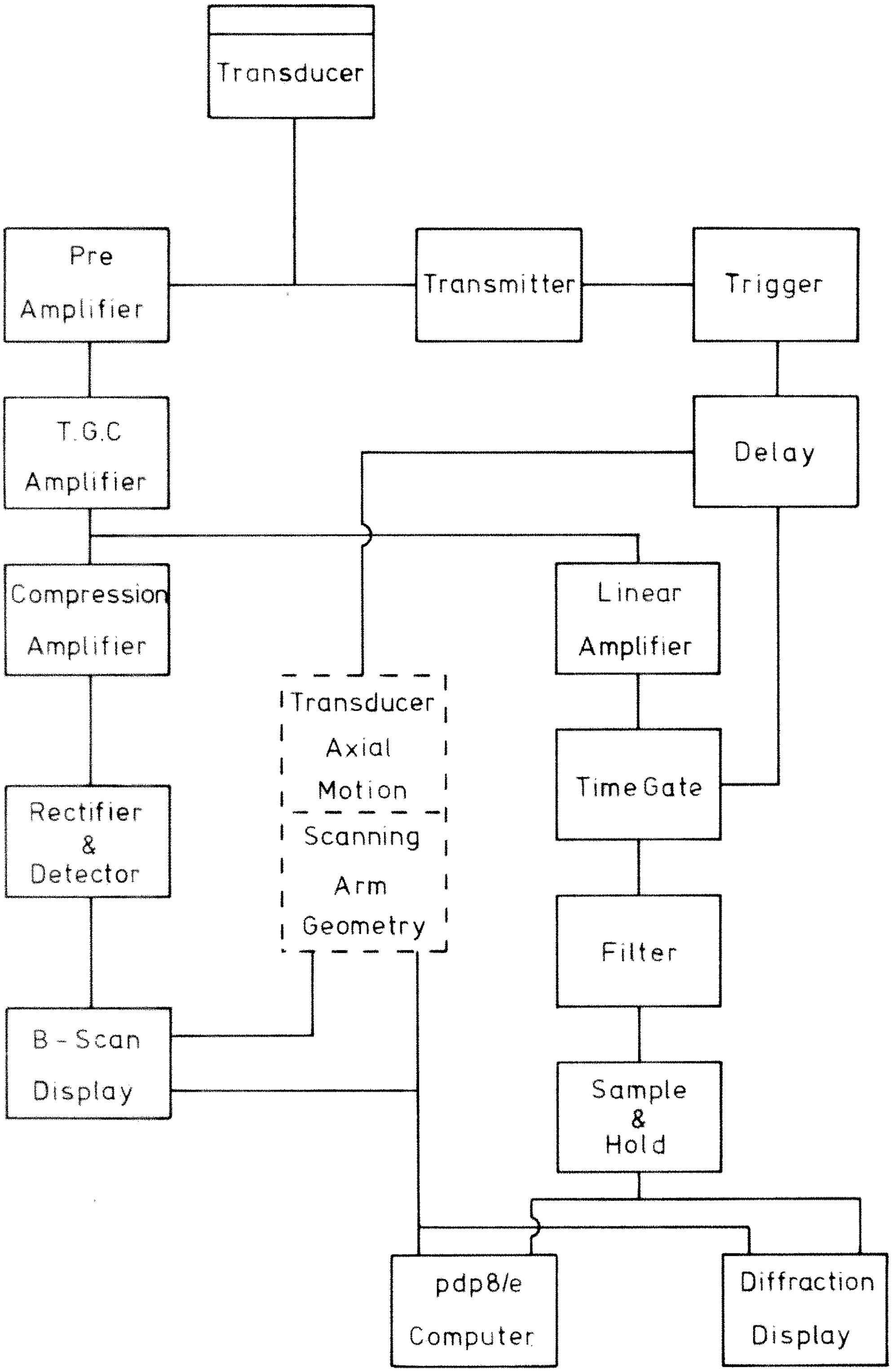

Fig. 2.

Schematic diagram of diffraction scanner electronics.

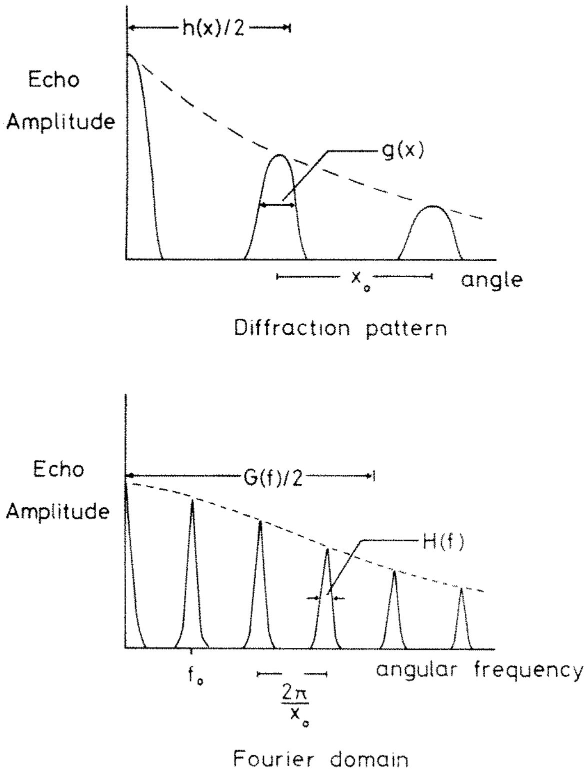

FIG. 3.

A hypothetical diffraction pattern and its Fourier transform indicating the inverse relationship between fine structure (peak shape) and coarse structure (trace envelope).

which, at first glance, appears to be just as complicated as the original diffraction pattern. Fig. 3 illustrates how the Fourier transform of specific angular information is portrayed as angular frequency information.

If the original diffraction pattern consists of the three specific features illustrated in Fig. 3 then each of these has its corresponding representation in the frequency domain. For example, any regular peak spacing (x_0) in the diffraction pattern transforms to a corresponding spectral frequency ($f_0=2\pi/x_0$) and harmonics. The width, g (x), of the diffraction peaks is related to the width of the spectral envelope, G (f), whilst any envelope or modulation of the original trace, with width h (x), is represented by the width H (f) of the spectral peaks. More complex patterns can usually be considered as multiple forms of these three basic parameters.

These three spectral parameters, f_0, G (f) and H (f), have been used as potential tissue signatures for the studies reported here.

RESULTS

Some preliminary diffraction patterns associated with human calf muscle, normal liver and a metastatic deposit in the liver were first reported by Huggins and Phelps (1977). Subsequently observations have been made on patterns from various tissues and pathologies (Nicholas, 1977). In this paper the results of a clinical trial involving 70 patients are presented. Investigations have been performed on two categories of disease best described as diffuse disorders and focal neoplasms. In the former case, organs which exhibit a uniform parenchymal echo pattern (though abnormal) on the conventional B-scan images are examined over as wide a region as possible with diffraction patterns being collected from randomly selected regions of the tissue. For the second case, regions of interest (suspected lesions) are first located using standard scanning techniques, and then diffraction patterns obtained from within the suspected lesions are compared with those from adjacent, supposedly normal, regions of tissue. As this latter case involves a differential analysis it permits an immediate appraisal of tissue normality.

Figures 4 and 5 illustrate, in detail, the procedure and results for one particular patient. In Fig. 4 the longitudinal B-scan of the patient showed an interesting area of about 4 cm diameter in the posterior region of the right lobe of the liver. The enlarged picture of this region indicated that it consisted of a ring of diminished echoes within which the echo pattern was visually indistinguishable from that of the supposedly normal adjacent parenchymal echoes. The clinical diagnosis based on this conventional scan and others was inconclusive as to whether this region was metastatic or normal. The ring of diminished echoes was suggestive of a "target" lesion but these usually display an abnormal pattern of internal echoes. When investigated with the diffraction scanner at a frequency of 2.5 MHz and with a 10 μs gate length, the region of interest produced a diffraction pattern which differed significantly from the scans associated with the supposedly normal regions (see Fig. 4). This difference, an increase in the number of diffraction peaks per unit angle of scanning movement, is typical of both the *in vitro* findings of Nicholas (1976) and previous *in vivo* results where similar patterns have been associated with neoplastic involvement. Confirmation of these findings was obtained on the following day when a liver scintigram, also illustrated in Fig. 4, clearly indicated the presence of a large single lesion in the posterior border of the right lobe of the liver.

Ultrasonic follow-up on this patient resulted in a

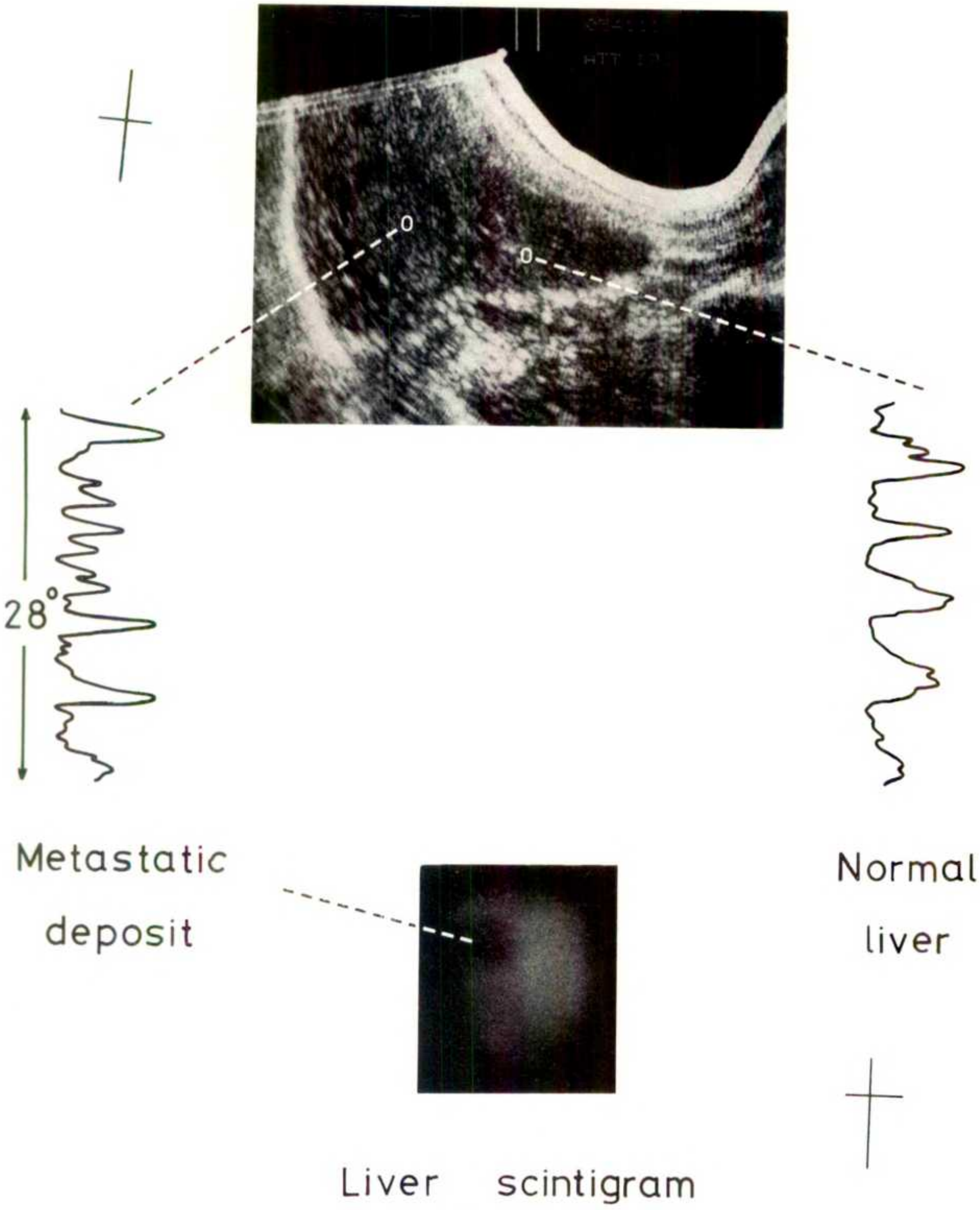

Fig. 4.

Longitudinal B-scan of the right lobe of the liver depicting an anechoic ring of approximately 3 cm diameter. Accompanying diffraction patterns and liver scintigrams (anterior view) confirm this as a solid lesion.

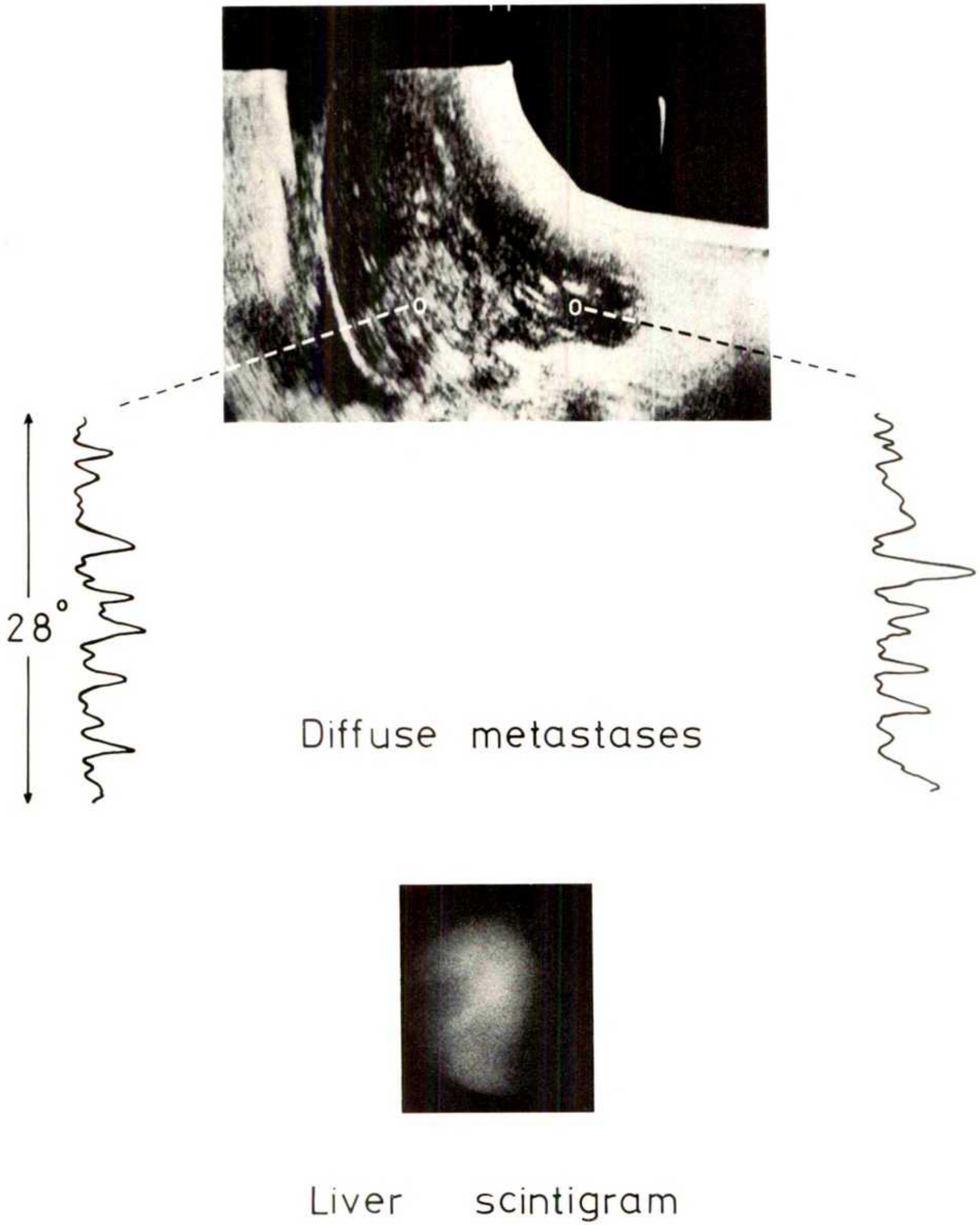

FIG. 5.

Same patient as in Fig. 4, repeat of scanning procedures three months later. All tests now suggest multiple diffuse metastases.

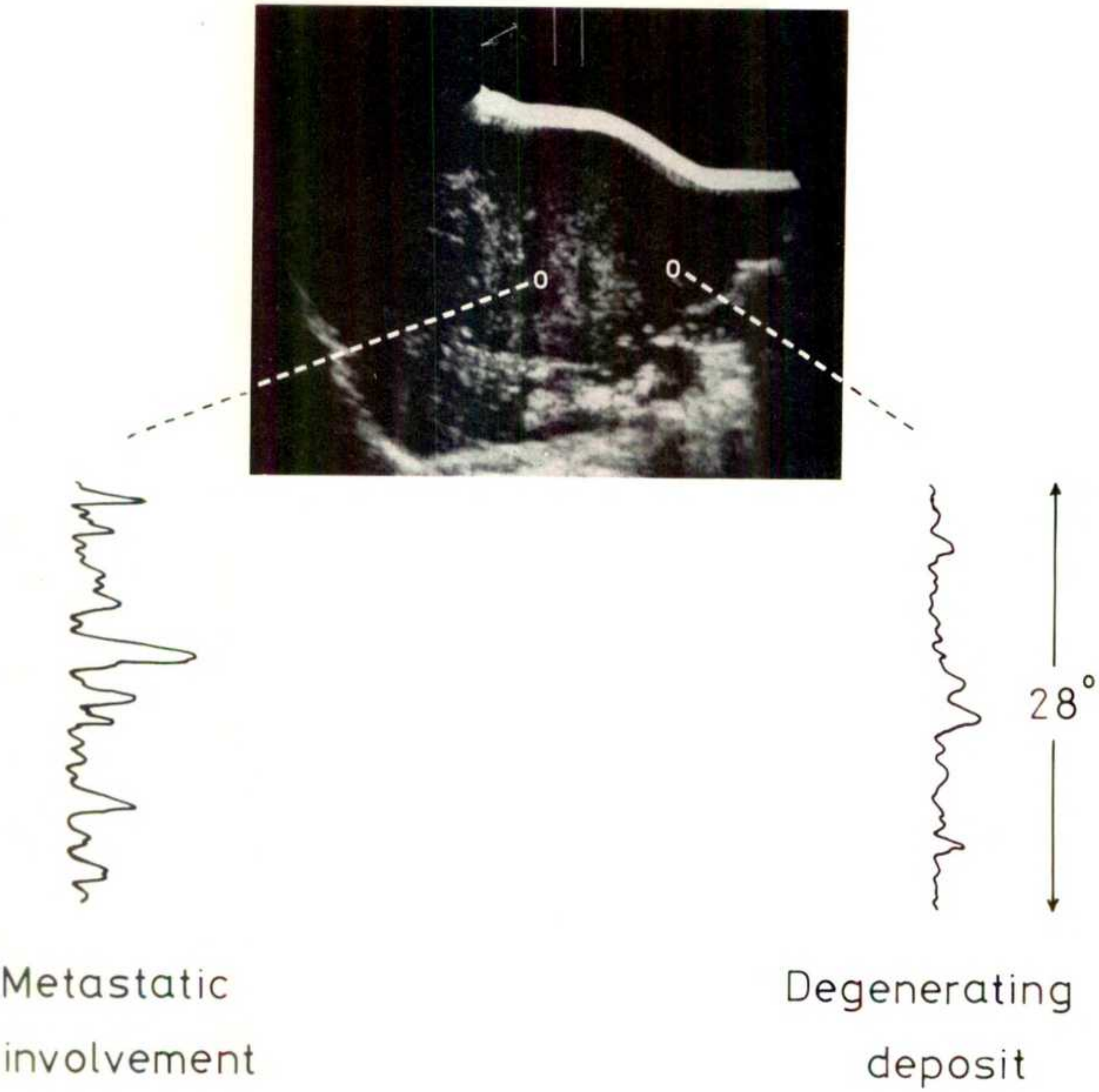

Fig. 6.
Liver scans from a patient with widespread malignant involvement and a lesion (cyst/degenerating deposit?) overlying the right lobe.

further examination three months later. The ultrasound B-scan, shown in Fig. 5, indicated that there was now widespread metastatic involvement of the liver: a finding which was confirmed by the use of the diffraction scanner and a liver scintigram. On this examination no diffraction patterns could be obtained corresponding to normal liver: all the patterns exhibited the increased number of diffraction peaks associated with metastatic involvement.

A further example is illustrated in Fig. 6. This patient presented a large abdominal swelling which, on investigation by conventional ultrasonic sector B-scanning, indicated a distinct mass in the right lobe of the liver. The ultrasonic appearance of this mass is that of an anechoic region interspersed with low echoes. As the boundaries of this mass are indistinct, one is left with at least two possible diagnoses; either the region is fluid-filled and contains debris—a possible congenital cyst—or it is a degenerating tumour which has reached a "jelly-like" stage. The diffraction patterns obtained from within this mass indicated that some degree of structure did exist which was stable in its positioning, i.e. the diffraction pattern was repeatable over short time intervals. As one would expect the debris floating in a fluid-filled region to alter its position with time, it is extremely unlikely that repeated scans in such anatomy would produce similar diffraction patterns. Confirmation that this was indeed a degenerating tumour was eventually achieved at post-mortem examination two months later.

These two cases illustrate that the diffraction technique is capable of assessing certain disease types, especially when a differential method can be employed. When it is used to complement existing diagnostic procedures it often produces a more specific categorization of the disease.

The examination of diffuse disorders of the liver presents a similar problem to that experienced using conventional ultrasonic techniques in that no internal tissue comparisons can be made. Thus one is forced to attempt a differentiation based upon the general appearance of the diffraction patterns associated with normal liver tissue in other individuals. Figure 7 shows examples of diffraction patterns obtained from normal liver tissue and from two diffuse pathologies: cirrhosis and diffuse lymphomatous infiltration. The diffraction patterns associated with the lymphoma involvement display the typical characteristics of neoplasms (an increased angular rate of variation in signal amplitude). At first glance, it appears that the cirrhotic tissue produces a trace similar to that of diffuse lymphoma infiltration. It is not until a more critical inspection of the traces is performed that a low-frequency (0.03 cycles per degree of angular movement) modulation of the traces becomes apparent. It is this feature which has occurred in 23 of the 28 diffraction patterns associated with five different cases of cirrhosis.

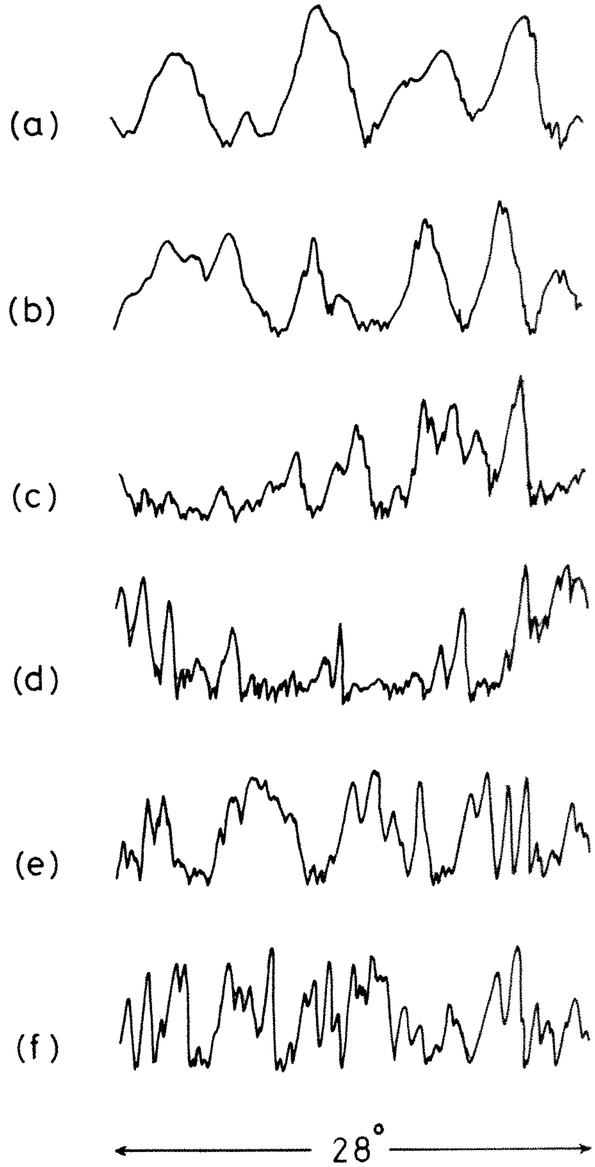

FIG. 7.

Typical *in vivo* diffraction patterns from normal and abnormal liver tissue performed at 2.5 MHz with a gate length of 10 μs and an angular scanning movement of 28°. (a) and (b) normal liver, (c) and (d) cirrhotic tissue, (e) and (f) diffuse lymphoma infiltration.

The main advantage of this method of tissue characterization is the ease with which the diffraction patterns can be quantified, thus eliminating the need for subjective evaluation. At present the diffraction scanner is connected on-line to a PDP/8e computer, enabling the patterns to be digitized and stored on magnetic disc. Several analytical approaches are obviously available for the quantitation of these scans and many have been discussed in detail elsewhere (Nicholas, 1978b). Our present approach, discussed previously, has been applied to all the 416 diffraction patterns reported here; examples of the amplitude, angular-frequency spectra derived from the diffraction patterns associated with various liver conditions are illustrated in Fig. 8. Table I lists the categories of liver disease examined by the diffraction technique to date. Confirmation of disease has been achieved by biopsy, surgery or post-mortem findings in 16 of the 48 abnormal livers. Of the remaining 32, 30 were examined by other techniques such as liver scintigraphy and X-ray computed tomography. These examinations and subsequent follow-ups certainly confirmed all the cases where a malignant condition was suspected, although the categorizations of specific secondary deposits may be open to question. This uncertainty has prompted the broad classification of non-cystic liver conditions into four classes: normal, neoplastic liver (including primary hepatoma, diffuse and focal secondary involvement), cirrhosis and secondary liver involvement associated with Hodgkin's disease. Unfortunately, our technique in its present form has proved to be incapable (using these parameters) of differentiating fatty or non-specific enlarged livers from normal.

Figures 9, 10 and 11 indicate the variation of the

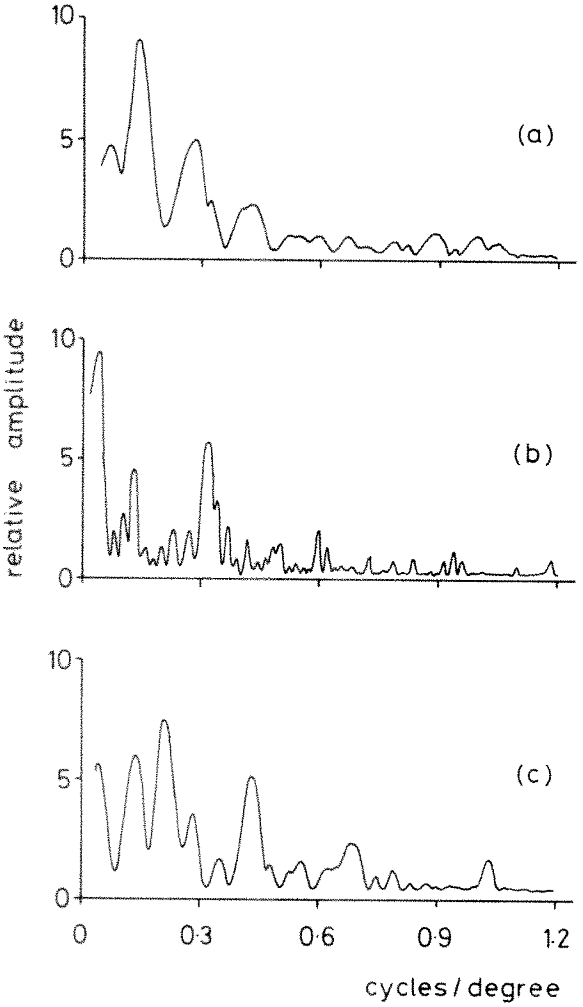

FIG. 8.

Typical amplitude angular-frequency spectra derived from the *in vivo* diffraction patterns associated with specific liver conditions. (a) normal tissue, (b) cirrhotic tissue, (c) diffuse lymphoma infiltration.

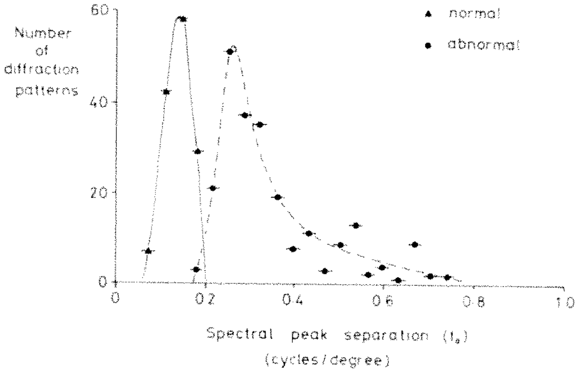

FIG. 9.

Graph of the positions, f_0, of the predominant peaks in the angular frequency spectra associated with normal ▲ and abnormal ● liver condtiions.

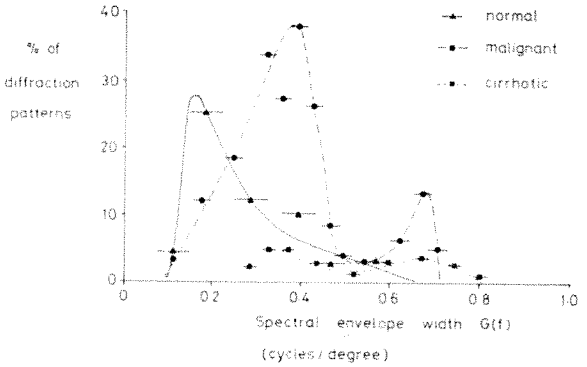

FIG. 10.

Graph of the predominant spectral envelope widths, G(f), associated with various liver pathologies: ▲ normal liver tissue, ● malignant pathologies (see Table I), ■ cirrhotic tissue.

three spectral parameters and their association with the classification of liver pathology. The angular frequency values of the predominant peaks (Fig. 9) proved capable of differentiating between normal and abnormal pathology though incapable of any finer classification. The envelopes associated with the predominant spectral peaks, illustrated in Fig. 10, still indicate an overall separation of normal and abnormal pathology although the main use of this parameter has been to achieve some additional degree of differentiation between cirrhosis and the neoplastic conditions, especially Hodgkin's disease. Although these diseases have only been examined in a limited number of scans (28 cirrhosis and 18 Hodgkin's respectively), they show a marked difference in spectral peak widths. The use of this parameter with the diffraction pattern envelopes (fine structure in the frequency domain), see Fig. 11, indicates that cirrhosis and Hodgkin's disease can quite easily be differentiated from all the other liver conditions reported here. Despite the relatively few cases examined the 416 diffraction patterns analysed indicate that definite trends exist.

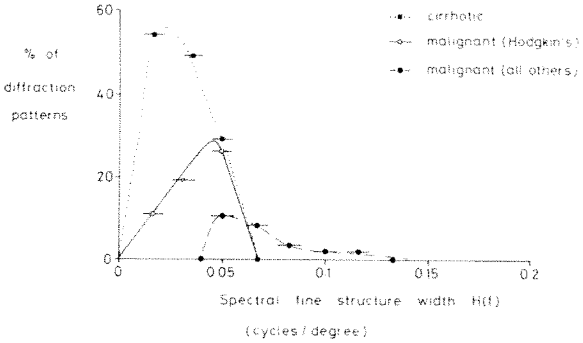

FIG. 11.

Graph of the spectral fine structure widths, H(f), associated with various liver pathologies: ■ cirrhotic tissue, ○ malignant secondary liver involvement (Hodgkin's), ● malignant liver involvement (all others—see Table I).

At present the angular frequency spectra are assessed by eye but it must be stressed that, for this study, all the spectra were analysed "blind" and only related to the known tissue pathology retrospectively. Work is in hand to computerize the whole analysis procedure.

DISCUSSION

Before summarizing the achievements of this new technique and its impact upon the categorization of liver pathology, consideration should be given to various factors relating to these diffraction patterns.

Skin contact and viewing window

The mechanical constraints of the scanning arm restrict the regions of the human anatomy which can be investigated. Thyroids (not reported here) and breasts can be best examined by using a standard water bath approach with the patient supine. The soft-tissue organs of the abdomen, however, can present some difficulty. The present machine is too cumbersome to permit investigations to be made under the costal margin and only the inferior portion of the liver can be assessed. Kidneys and the spleen are usually easily scanned. Bowel gas is a major limitation as the geometry of the scanning arm does not allow gassy regions to be circumvented. The problems of skin contact limit the scanning

TABLE I

SUMMARY OF LIVER CONDITIONS EXAMINED *IN VIVO*

Pathology of primary tumour	Liver findings	Number of cases	Number of diffraction patterns
Normal	Normal	22	135
Teratoma	Focal metastases	3	19
Melanoma	Focal metastases	1	6
	Diffuse infiltration	3	17
Lymphoma	Focal metastases	1	6
	Diffuse infiltration	3	18
Sarcoma	Focal metastases	1	7
Carcinoma	Focal metastases	12	70
	Widespread infiltration "patchy"	5	26
	Hepatoma	3	18
Hodgkin's	Focal metastases	3	18
	Cirrhosis	5	28
	Fatty liver	3	19
	Hepatomegaly	5	29
		70	416

angle to a maximum of 35°, though this has proved to be sufficient in terms of data acquisition. Clearly, some of these problems are specific to our existing prototype equipment rather than being inherent in the underlying principles of the approach.

Differing sound paths

When a specific tissue volume is investigated over a range of aspect angles there will evidently be variations in the sound paths through overlying tissues, and such differences may influence the corresponding values of ultrasound velocity and attenuation. When using a fixed time-delay any such velocity differences will result in a shift in the tissue volume being examined as the transducer is moved across the patient's skin surface. Although this can undoubtedly occur, its significance is probably small. If the diffraction patterns were predominantly caused by velocity variations then one would expect a fairly random distribution of patterns—a situation which is not consistent with our results to date. Variations in attenuation will undoubtedly occur; however, knowledge of the attenuating properties of human soft tissues suggests that the overall effect is unlikely to cause more than a few decibels variation in received signal strength. As inspection of the diffraction patterns indicates that at least 30 dB of useful information is being collected so it is probable that attenuation variations will only contribute a minor uncertainty to the patterns produced.

Tissue movement

Although all patients were scanned under conditions of full inspiration, local tissue movement associated with the cardiac cycle could not be eliminated. It was, therefore, necessary to repeat every diffraction pattern associated with a specific tissue volume in order to check that the basic pattern remained unchanged. If sufficient correlation between successive scans was not achieved, then those scans were eliminated from our study. In total, some 22 patients have proved to be impossible to scan by this technique simply due to tissue movements, and they have been eliminated from this study. This represents a serious problem in diffraction scanning which will only be overcome by developing a system that can operate in "real time", in the sense of collecting a diffraction pattern within a few milliseconds.

Conclusion

The results presented here can be summarized according to the method of scanning and disease state. Where a differential method can be applied, as in focal disorders of the liver, the technique involves making a diffraction record within the focal abnormality and comparing this with the corresponding record for, supposedly, normal liver tissue. In this situation a 95% success rate was achieved in determining the malignant state of the abnormality. Only two cases were incorrectly classified as normal and in each case only a single deposit of diameter between 1.5 and 2.5 cm was involved. The error in diagnosis in these cases may well have been associated with incorrect positioning of the scanning arm and consequent failure to locate the suspected region.

The technique also seems particularly useful in differentiating between fluid-filled lesions (containing debris) and degenerating tumours, both of which can produce similar appearances on conventional sector B-scans. The diffraction patterns associated with the former are non-repeatable due to the motion of the debris within the lesion, whilst the latter present some degree of rigidity in structure and thus give patterns which exhibit some repeatable features.

The use of diffraction scanning to characterize specific diffuse disorders has met with varied degrees of success. Diffuse neoplastic liver involvement is easily characterized, with diffraction patterns similar to those associated with focal neoplasms. So far a 100% success rate in detecting malignant infiltration of the liver has been achieved in our investigation of 11 cases (including five cases of widespread "patchy" metastatic involvement (see Table I)) involving 61 diffraction patterns. Of the other types of diffuse disorder only cirrhotic tissue has yet produced a specific disease signature, where a single-cycle modulation of the diffraction pattern occurs. Although many patterns have been collected, the variations in disease types have resulted in too few examinations of specific tissue pathologies to do other than group them into broad categories. It is to be hoped that when a larger set of data has been accumulated a more specific differentiation of tissue tissue abnormalities may prove possible.

Many problems specific to *in vivo* studies must be investigated before the true potential of this technique can be realized. Parametric studies of quantities such as transmit pulse length, frequency and volume size are at present being performed, whilst an evaluation of the effects of intervening tissue layers of muscle, fat and skin has yet to be performed.

The clinical value of our present apparatus can only be postulated at this stage, but the results indicate that it is capable of providing useful quantitative data to complement the high quality grey-scale scans that are at present attainable.

ACKNOWLEDGMENTS

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Book reviews

Handbuch der Medizinischen Radiologie (Encyclopaedia of Medical Radiology). Roentgen Diagnosis of the Heart and Blood Vessels. Part 2c. (Volume X). By H. Gremmel, K. Kaiser, H. H. Löhr and H. Vieten, pp. ix+421, 1979 (Springer-Verlag, Berlin), DM 60/$33.00
ISBN 3-540-08831-8

The first 155 pages deal with open injuries, while another 183 pages deal with blunt trauma to the heart and adjacent great vessels. Each section is followed by a comprehensive list of references. The subject index is reproduced in German and English.

There is a full discussion of both the acute and chronic effects of trauma to each heart chamber and of the various ways of investigation. The illustrations are technically good but disappointing in number and material illustrated. Every conceivable fistula and vessel rupture is discussed in the text but with very few illustrations. There is a good section on the catheter removal of foreign bodies from the great vessels and a very good discussion of the aetiology of traumatic rupture of the aorta and its branches. The authors make the important points that damage to the great vessels may not become clinically evident for months or even years after the trauma and also that the great vessels should always be included in the investigation when trauma to the heart is suspected. A persuasive diagram illustrating the benefits of wearing car seat belts is included.

The book is interesting but appears to be more slanted to the clinician than the radiologist, who would expect more illustrations of the radiology of the conditions discussed.

G. M. STEINER.

Multiple Imaging Procedures. No. 1. Pulmonary system Practical approaches to pulmonary diagnosis. Edited by S. S. Siegelman, F. P. Stitik and W. R. Summer, pp. xi+372, 1979 (Grune & Stratton Inc., New York). $33.75.
ISBN 0-8089-1143-0.

This book is aimed at radiologists who practise as diagnostic physicians rather than as photographers. It is a multi-author volume (there are 15 contributors) compiled by clinicians involved in thoracic disease at Johns Hopkins Hospital. Two of the three editors are radiologists. The uniformity of style and opinion says much for the working relationship that must exist at that centre. In modern medical practice clinicians frequently find themselves confronted with a plethora of diagnostic "aids" and choosing the correct tests in the best order is—or can be—very much the name of a game often well umpired by radiologists.

Chapters in this book include: The role of radionuclide studies in the diagnosis of pulmonary disease; Biopsies of the lung; Efficacy of various techniques for diagnosing pulmonary emboli; and Pulmonary disease in the immunocompromised host. An individual account is offered of how these diagnostic problems are best solved. That this is based on a local collective experience makes it all the better reading—and for those who cavil there are plenty of references to argue with.

I found it very enjoyable reading and will be surprised if other clinicians dealing with chest disease do not find it equally so. It obviously needs to be bought soon—whilst it is still at a reasonable price and before it becomes out-of-date.

C. D. R. FLOWER.

1979, *British Journal of Radiology*, *52*, 962–967

The absorbed dose in the vicinity of an interface between two media irradiated by a ^{60}Co source

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ABSTRACT

Monte Carlo techniques are used to generate the distribution of absorbed dose in the vicinity of an interface between two media. Computer-generated distributions for absorbers comprising the media carbon-copper, water-aluminium and aluminium-water are presented. The features of the distributions in regions of electron equilibrium and non-equilibrium, in particular finite discontinuities at the boundaries and subsequent build up or build down, are discussed both qualitatively and quantitatively. The difficulties inherent in interpreting ionization measurements in the neighbourhood of interfaces are outlined.

It has been known for some time that in the vicinity of an interface between two media of differing atomic number irradiated by a photon beam travelling normal to the interface, a local variation in absorbed dose takes place (Dutreix and Bernard, 1966). This variation is confined to the regions (hereafter referred to as the transition regions) of electron non-equilibrium which exist on either side of the interface and whose thickness is of the order of the range of the maximum-energy secondary electron which it is possible to liberate. It arises because both the spectrum of secondary electrons arising in the media and their rate of energy loss are different for the two media. In addition electrons may originate in one material but deposit some of their energy in the other, after crossing the interface. The effects of this behaviour on the absorbed dose are superimposed within the transition regions on the large scale dose distribution in the two media arising from their differing photon absorption and scattering properties. The bulk dose distributions in inhomogeneous media can be described by a variety of techniques (ICRU 24, 1976); this paper is largely confined to the problem of describing the dose distribution in the transition regions.

An understanding of the dose distribution in the vicinity of the interface has recently assumed greater significance now that computerized tomographic data are being used to perform dosimetry taking account of the detailed topography of tissue inhomogeneities (Parker *et al.*, 1979). For ^{60}Co γ-radiation the transition region has a thickness of the order 0.4 g cm^{-2} and so for tissue densities close to that of water, interface effects are confined to within only a few millimetres of the interface. For high energy radiations of the order of 25 MeV and low density tissues, however, the variations can extend to a few centimetres either side of the interface.

PROBLEMS INHERENT IN DETERMINING THE DISTRIBUTION OF ABSORBED DOSE IN THE VICINITY OF AN INTERFACE

To date, the majority of experiments designed to investigate the behaviour in the transition region have yielded measurements of the ionization in air-cavity chambers located at or near the interface between different media. Attempts have then been made to deduce the distribution of absorbed dose from such measurements. In doing this, some limiting assumptions have been made. These are discussed in this section and the need for direct measurement or calculation of absorbed dose is justified.

Observations of ionization in an air cavity have been reported by Wingate *et al.* (1962), Drexler (1968), Dutreix *et al.* (1962; 1964) and Dutreix and Bernard (1966). In particular the latter authors have reported the ionization distributions close to a copper–carbon and carbon–copper interface. In the last paper referred to, the results have been translated from ionization measurements into a prediction of the absorbed dose in an infinitesimally small volume of water located within either the copper or the carbon. To do this the data have been adjusted via the mass stopping powers for the two media in a manner recently clarified by Darley (1979). As Darley points out, however, this conversion is valid only where electronic equilibrium has been re-established, *i.e.* outside the transition region, and should not have been applied to the whole curve of Dutreix and Bernard (1966). If this interpretation of the ionization measurements is made, then the ratio of the equilibrium dose in an infinitesimally small volume of water within copper to that within carbon is 1.45. By using the mass stopping powers and mass energy absorption coefficients for copper and carbon, this ratio was deduced theoretically by Darley (1979) and shown to be in almost exact agreement with the observations.

It is however the ratio of the doses to a small mass of copper and to a small mass of carbon which is of interest rather than the above ratio. It has been shown by Lowe (1978) that this can also be calculated from the ionization data of Dutreix and Bernard (1966) via the mass stopping power ratios for copper and carbon relative to air, although only under equilibrium conditions. The value obtained for the ratio is 1.03. Lowe claims that this is in substantial agreement with a predicted value of 0.92 found from the ratio of the narrow-beam mass-energy absorption coefficients of copper and carbon at 1.25 MeV.

Within the transition regions, however, such conversions of ionization data to absorbed-dose data are currently not possible, since the electron slowing-down spectra and stopping-power ratios near an interface are not known. At each location within the transition regions there exist electrons which have crossed the interface and whose energies are a function of the scattering properties of both media. Berger (1971a) has suggested that the parameters needed to perform the conversion from ionization to absorbed dose within the transition regions could plausibly lie between the corresponding values for each homogeneous medium. For the example of a gold–aluminium interface, quoted by Berger (1971a), the gold-to-air electron mass stopping power ratio $S_{\mathrm{air}}^{\mathrm{gold}}$ is 0.498, whilst $S_{\mathrm{air}}^{\mathrm{aluminium}}$ is 0.857. The average of these two values differs by 35% from the smaller value, namely $S_{\mathrm{air}}^{\mathrm{gold}}$. For a carbon–copper interface the stopping power ratios under electronic equilibrium are $S_{\mathrm{air}}^{\mathrm{carbon}} = 1.023$ and $S_{\mathrm{air}}^{\mathrm{copper}} = 0.674$. The average of these two values differs by 25% from $S_{\mathrm{air}}^{\mathrm{copper}}$. These figures are taken to indicate that such average values cannot be used to convert ionization data to absorbed-dose data in the transition regions.

All these difficulties would be avoided if absorbed dose could be directly measured or calculated. Adadurov and Lazurik (1977) have presented numerical calculations of the dose distribution at the interface of five separate media with aluminium. Berger (1971a) presented similar calculations for the carbon–copper interface but displayed the data in a way which is not easy to compare with the converted form of the ionization data of Dutreix and Bernard (1966). In addition, Wall and Burke (1970) claim to have measured dose distributions at interfaces with aluminium and gold using a multiple plate ionization chamber.

In this paper the results of a Monte Carlo calculation of the distribution of absorbed dose in the vicinity of a carbon–copper interface are presented. Beyond the transition region the results may be compared with those of Dutreix and Bernard (1966). Within the transition region the behaviour can be explained qualitatively.

MONTE CARLO COMPUTATION OF THE ABSORBED DOSE IN THE VICINITY OF AN INTERFACE

A Monte Carlo computer program has been constructed which traces the passage of a parallel beam of ^{60}Co radiation of square cross-section (1×1 mm^2) into a large cube of absorber comprising two layers of differing materials. The axis of the beam is normal to the interface between the two media. In the model each photon is considered separately in turn as it interacts with the media. The distance between interaction sites is governed by the narrow-beam linear attenuation coefficient whilst the nature of collisions, whether Compton, photoelectric or pair production, is determined by a random-number generator in conjunction with the known cross sections for each interaction. The accuracy of the cross-sectional data and theoretical equations used to derive the history of each photon has been established by comparison of Monte Carlo results and experiment in a different context (Webb and Parker, 1978). After an interaction any secondary Compton photons are followed to their next collision and secondary electron histories are recorded. Electrons are assumed to deposit their energy along their range according to the Bragg curve in the material, and in this manner central-axis and off-axis absorbed-dose distributions can be computed as a function of depth within the absorber. The data of Pages *et al.* (1972) were utilized and it was assumed that each electron deposited its energy along the straight line track. Berger (1971b) has presented data in which the range of an electron of known energy is given in terms of the radius of a sphere in which 90% of the electron energy is deposited. In these calculations a straight line track of energy deposition is not assumed. A comparison of the range–energy data of Pages *et al.* (1972) and Berger (1971b) showed that for electrons in the range 0.05 to 4 MeV the data are in substantial agreement.

In order to compute absorbed-dose distributions for finite area beams a technique has been developed by which an integration is performed over however many sub-beams of area 1×1 mm^2 are needed to create the beam of finite area. The advantage of this technique is that the accuracy of the calculation is not degraded as the beam area increases. More extensive details of the model are documented elsewhere (Webb and Parker, 1978; Webb and Fox, 1979a; b) when the computation procedure was applied to large-scale dose distributions. In the present application the distribution of absorbed dose is recorded in intervals of 0.25 mm either side of the boundary. In order to compute and display the absorbed dose in equilibrium regions each absorber is 12.5 mm thick. Narrower spatial intervals are desirable but precluded if the results are to be relatively unlimited by statistical noise.

Results and Discussion

Figure 1 displays the distribution of absorbed dose for a 10 × 10 cm^2 ^{60}Co beam incident on a carbon–copper interface. At the entrance surface of the carbon the dose builds up to a maximum in about 2 mm, thereafter decreasing slightly due to photon absorption. On the copper side of the interface (referred to subsequently as the downstream side) and within the transition region, the distribution reaches a minimum before subsequently building up to a new maximum in copper at about 1 mm from the interface. The transition region has a thickness of the order 0.4 gm cm^{-2}. The qualitative behaviour in this region is in agreement with the observations of Adadurov and Lazurik (1977) who deduced that in passing from a medium of lower to higher atomic number, the beam delivers an absorbed dose which is smaller at first than the equilibrium value, leading to a maximum appearing on the distribution at a distance from the boundary approximately equal to the mean-free path for electrons of maximum energy. Wall and Burke (1970) observed similar qualitative behaviour experimentally. It is tempting to form a ratio of the equilibrium absorbed doses in copper and carbon just at the boundaries of the transition regions furthest from the interface. This ratio is 1.03 and agrees with Lowe's conversion of the ionization data of Dutreix and Bernard (1966) to absorbed dose in the equilibrium region. Both these results disagree by 11%, however, with a prediction of 0.92 based on the ratio of narrow-beam mass-energy absorption coefficients at 1.25 MeV for copper and carbon. It is suggested that this ratio may not fully describe the behaviour in the equilibrium region which is likely to be dependent on the beam area. The accuracy of the Monte Carlo technique was verified by inspecting the central axis depth dose distribution for the beam of area 1 × 1 mm^2 intersecting the carbon–copper interface. At the boundaries of the transition regions furthest from the interface the ratio of the equilibrium absorbed doses in copper and carbon is 0.91. The difference of only

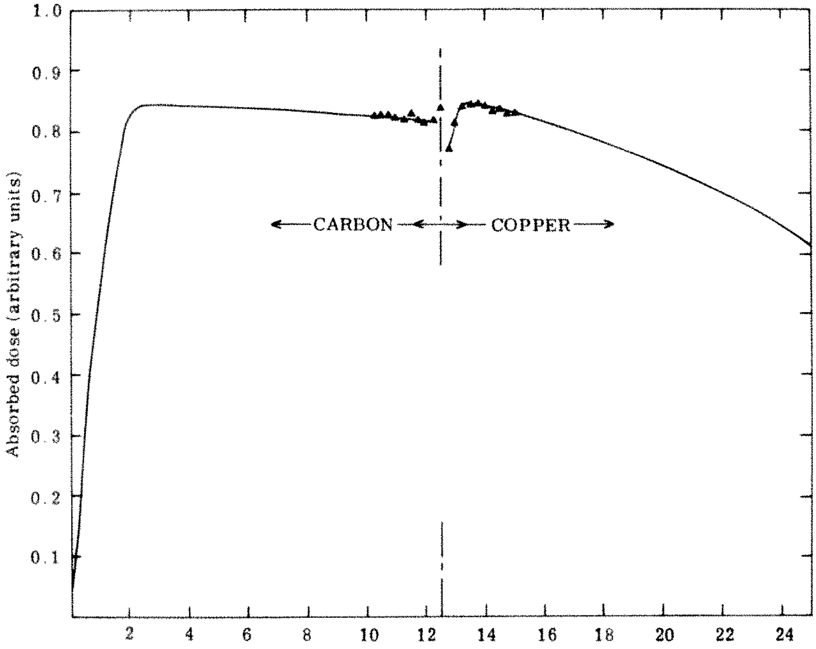

Fig. 1.

The distribution of absorbed dose for a 10 × 10 cm^2 ^{60}Co beam incident on a carbon–copper interface. The points in Figs. 1–3 close to the interface are indicated by ▲ to demonstrate the magnitude of statistical fluctuations.

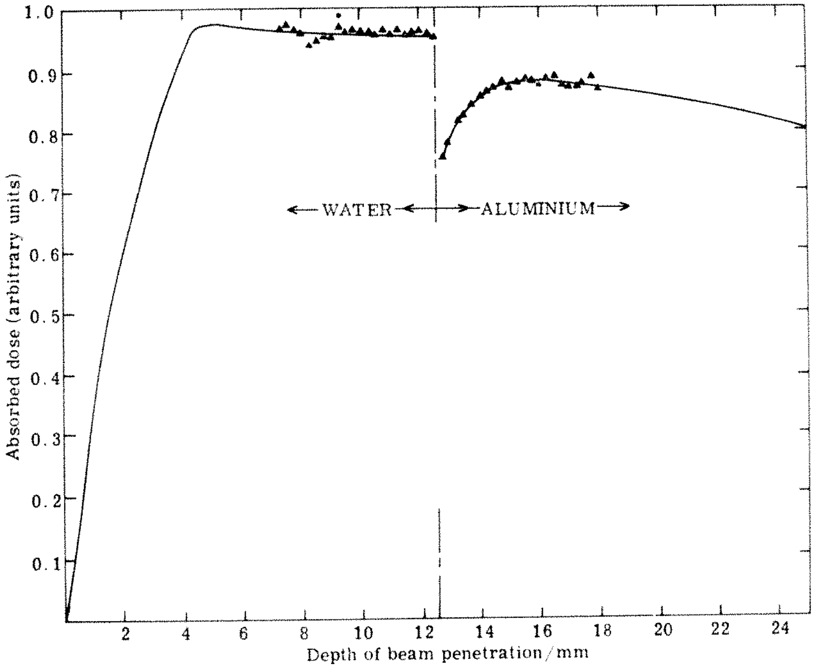

Fig. 2.

The distribution of absorbed dose for a 10 × 10 cm^2 ^{60}Co beam incident on a water–aluminium interface.

1% from the prediction of 0.92, based on the narrow-beam mass-energy absorption coefficients at 1.25 MeV, is a measure of the (small) uncertainty inherent in the Monte Carlo data.

At the interface itself, the ratio of the absorbed doses just on either side of the boundary must be the same as the ratio of the mass stopping powers of the two media, since the electron spectra at these locations are the same. It is difficult to test this hypothesis using the Monte Carlo data owing to the difficulty of interpolating the dose at the boundary, but just within the copper, from the adjacent data points.

Figure 2 presents similar data for a water–aluminium interface and similar qualitative features are observed. The scale lengths of the initial build-up region and transition regions are of course different. The observed ratio of absorbed doses in the equilibrium regions in water and in aluminium is 1.09. Figure 3 presents data for a reversed configuration in which the beam initially penetrates the aluminium. Water can be considered to have an effective "atomic number" of 7.4; hence for the configuration in Fig. 3 the downstream medium has the lower atomic number. In this case the distribution is enhanced in the downstream (water) medium in agreement with the statements of Adadurov and Lazurik (1977). The observed ratio of absorbed doses in the equilibrium regions in water and aluminium is again 1.09. The ratio of narrow-beam mass-energy (1.25 MeV) absorption coefficients is however 1.15, and is 6% in disagreement.

Once more it is difficult to interpolate the dose close to the downstream side of the interface, and a comparison with the mass stopping power ratio in the two media is not possible. However, the general behaviour of discontinuities observed at the interfaces in these Monte Carlo computations are as expected, and in the transition region the distribution of absorbed dose progresses smoothly from the discontinuity to the new equilibrium region.

Conclusions

Monte Carlo techniques have been used to generate the distribution of absorbed dose in the vicinity of an interface between water and aluminium and between carbon and copper for a 10 × 10 cm^2 beam of ^{60}Co radiation. It has been observed that superimposed on the large-scale features of the distribution which reflect the difference in attenuation and scattering properties of the media on either side of the interface there is a perturbation in the transition region. Just to the downstream side of the interface the absorbed dose exhibits a downwards

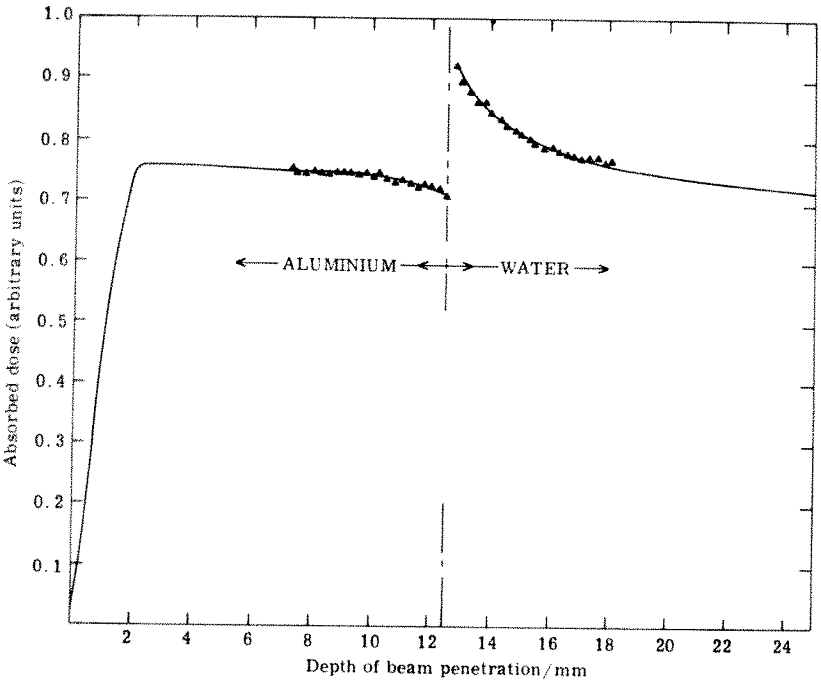

FIG. 3.

The distribution of absorbed dose for a 10 × 10 cm^2 ^{60}Co beam incident on an aluminium–water interface.

discontinuity if the downstream medium is of higher atomic number, and an upwards discontinuity if the downstream medium is of lower atomic number. Within the transition region the absorbed dose exhibits a monotonic rise or fall from the point of the discontinuity to a new equilibrium level. It has been shown that the ratio of equilibrium levels in the two media is however not the same as the ratio of the narrow-beam mass-energy absorption coefficients for the media at 1.25 MeV. Moreover, the precise height of the discontinuity, which can be predicted using the mass stopping powers in the two media, is difficult to verify by interpolating in the Monte Carlo data. The qualitative features within the transition region are in agreement with the theory of Adadurov and Lazurik (1977) although no general quantitative theory is currently available for comparison. It is erroneous to deduce the distribution of absorbed dose in the transition region from measurements of ionization, because the electron spectra and stopping-power ratio are known only for homogeneous media in electron equilibrium. The problem of determining the behaviour in this region, whilst clarified by the numerical calculations presented here, should receive further experimental attention. Such experiments must be designed to determine with fine resolution the absorbed dose rather than the air-cavity ionization.

ACKNOWLEDGMENTS

I am grateful to Dr. Richard Fox in collaboration with whom the Monte Carlo integration computer programs were developed. I should like to thank my colleagues Dr. Roy Parker and Miss Lea C. de Freitas for stimulating discussions.

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Book reviews

Atlas of Xeroradiographic Anatomy of Normal Skeletal Systems. By J. N. Wolfe, C. C. Kapdi and H. S. Murphy, pp. xiii+193, 93 illustrations, 1978 (Charles C. Thomas, Springfield, Illinois, USA), $29.50.
ISBN 0–398–03715–9.

This book is basically an atlas of radiographic anatomy of the skeletal system. As such, it is not unique. Its claim to originality is that it is an atlas of xeroradiographic anatomy.

Radiologists have come to expect first-class publications from John Wolfe and his publisher, Charles C. Thomas. Once again this team, with co-authors Kapdi and Murphy on this occasion, have produced an excellent book containing superb images, beautifully reproduced and painstakingly labelled. The wide recording latitude of the xerographic process shows osseous, articular and soft tissue structures clearly, all of which are annotated.

The work is divided into three parts. The first part consists of an historical review of xeroradiography and chapters on the xerographic process and image chacteristics. The process is simply and clearly described. Unfortunately there are inaccuracies on page 17 in the paragraph on "Image Density". The word "selenium" is used on three occasions and is incorrect on each occasion. Density control determines thickness of plastic, "toner" powder on the plate and *not* selenium.

The second and third parts record the anatomy of the axial and appendicular skeletons. In addition there are brief notes on radiographic positioning and useful tables of xeroradiographic and radiographic factors for each projection.

The quality of the atlas as a whole is excellent. The account of the xeroradiographic process, the detailed anatomical labelling and brief indication of radiographic factors and positioning make the atlas a very useful manual for radiographers and for medical students studying anatomy. It is particularly useful for the F.R.C.R. Part I examination and should therefore be found in the departmental libraries of all training establishments.

I. H. GRAVELLE.

Radiographic Techniques Related to Pathology. 2nd Edition. By M. A. Clifford and A. E. Drummond. pp. 77, 1977 (John Wright & Sons Ltd., Bristol) £2·00.

This useful book, being 100 mm × 165 mm, is of a size which can be carried around in the pocket of the radiographer's uniform.

As the preface says, this book is intended as a pocket guide to X-ray staff where full-time radiological advice is not available. It lists, alphabetically, various common and uncommon pathological conditions followed by a brief description of each and the plain films which may be required to demonstrate each condition.

The book includes many of the rarer pathologies a radiographer is likely to encounter in the X-ray department but, unfortunately, some of the more common ones *e.g.* pulmonary embolus, seem to be missing. The plain radiographic techniques listed are comprehensive and, often, the radiographer must select the most important views to include; for instance for intestinal obstruction, or perforated gastric ulcer three views of the abdomen are listed but the important erect view of the chest is omitted. These criticisms were mentioned in a review of the first edition and I wonder why the authors have not altered the text for the second edition.

It is perhaps unfortunate that this second edition was printed at the time when diagnostic imaging techniques were changing so rapidly and the value of suggesting the patient is referred for ultrasound or isotope scanning have not been mentioned. Sometimes these techniques are more valuable diagnostic aids while reducing radiation dose to the patient.

It is extremely difficult to include in a book of this size a comprehensive, yet selective, list of pathologies and optimum radiographic views to demonstrate them; I feel, despite the minor criticisms above, that this book is a worthwhile purchase for radiographers who do not have the benefit of full-time radiological advice.

F. A. PARIS.

1979, *British Journal of Radiology*, 52, 968–971

A simplified method of monitoring muco-ciliary transport

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ABSTRACT

A radioactive powder, formed by drying $^{99}Tc^m$ sulphide colloid, was used as a tracer to determine both lung clearance and tracheal mucosal transport of inhaled particles simultaneously in normal and bronchiectatic subjects. No change in either parameter with posture was noted in normal subjects, but patients with bronchiectasis exhibited rapid lung clearance when supine and slow clearance when erect, demonstrating the inefficient muco-ciliary transport in these patients. The method seems of value in monitoring the progress of bronchiectatic patients.

There are several lines of defence preventing deposition of inhaled particulate material in the lungs. Large particles, greater than 5 μm, are removed in the nasal cavity and the nasopharynx (Proctor, 1964), while very small particles, less than 0.1 μm, remain suspended as an aerosol and are exhaled with little deposition (Muir and Davies, 1967). Between these sizes the particles are deposited in the tracheo-bronchial tree and are normally cleared by entrapment in the mucus which is propelled toward the larynx by cilial action.

This muco-ciliary transport system is impaired in various disease states, and has been studied by measurement of airway clearance of inhaled particles (Morrow *et al.*, 1967), the results of which depend on the depth of penetration of the particles into the tracheo-bronchial tree, particles deposited in the proximal zones showing more rapid clearance. Markers have been used on the mucosal lining and their motion observed directly (Sacker *et al.*, 1973), but this is invasive, involving bronchoscopy, and the markers are large and thus non-physiological.

This study describes a simpler method of measuring both airway clearance and muco-ciliary transport, and presents the results obtained with postural changes in both healthy and bronchiectatic subjects.

METHOD

To obtain a radioactive particulate material within the "physiological" size range, $^{99}Tc^m$ sulphide colloid, prepared by the method of Larsen (Larsen and Nelp, 1966), was dried and crushed to give a fine powder which proved to have a particle size range between 0.02 μm and 5 μm by electron microscopy, thus corresponding to the anticipated size distribution deposited under normal conditions. This powder, after encapsulation, was inhaled by the subject in a single maximal inspiration using a turbo-inhaler.* Typically 1 ml of $^{99}Tc^m$ sulphur colloid suspension was dried, giving approximately ten million particles containing 0.5 mCi of activity. This proved adequate, even in bronchiectatic subjects, to produce lung-field images using a large-field gamma camera and was estimated using MIRD tables to give a maximal radiation dose of 680 mR to the trachea assuming no clearance, and usually less than 10 mR. The resulting radionuclide distribution was recorded for approximately 30 minutes on a dedicated mini-computer,† and areas of interest were selected over upper and lower zones of both lungs. The resulting time-activity curves were fitted to single exponentials, decay corrected, and clearance half-times were determined. In most studies with healthy subjects distinct foci of radionuclide were seen to move along the trachea, and the velocity of this movement, which reflects mucus-layer movement, was measured. This was accomplished by selecting a series of areas of interest along the trachea, calibrating their separation with radioactive markers on the camera collimator, then determining the arrival time of the foci of radionuclide at each area (Fig. 1).

RESULTS

Studies on eight healthy subjects measured in the supine position showed a great variation in the half-time for whole-lung clearance, varying from 40 minutes to 240 minutes (Table I); however, four studies on the same individual showed less than 8% variation in clearance half-time indicating satisfactory reproducibility. In all cases there was no significant difference in clearance rate between upper and lower zones of the lungs. Mucosal velocity was estimated in this way in seven of the eight subjects, again showing wide variation. In four subjects the mucosal velocity was relatively constant, decreasing slightly near the larynx. In the remainder the velocity was highly variable, the foci moving upward and downward in an irregular manner which was not associated with coughing or other disturbance. The mean velocity varied from 2 mm/min to 17 mm/min over the seven subjects, with a mean value of 9 mm/min. This seems rather slower than the values reported by Friedman *et al.* (1977) using Teflon discs, but faster than those reported by Yeates *et al.* (1975) using ^{99}Tc^{m} labelled microspheres. The study was repeated in the erect position with three of the subjects. In all cases there was no significant difference from the previous supine studies in overall clearance from the lungs, differential clearance between upper and lower zones of the lung, or tracheo-mucosal velocity.

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*Spinhaler, Fisons Ltd, Loughborough, Leicestershire, England.

†ADAC, Analytical Development Associates Corp., Sunnyvale, CA 94086, USA.

TABLE I

SPREAD OF HALF-TIMES FOR WHOLE-LUNG MUCO-CILIARY CLEARANCE IN NORMAL SUBJECTS

Subject	Clearance half-time (min)	
	Left lung	Right lung
1	240	115
2	100	143
3	116	162
4	71	178
5	40	70
6	47	41
7	41	64
8	163	107

The method was also applied to four patients with bronchiectasis, initially in the supine position and subsequently erect. In all cases the clearance of tracer from the lungs was abnormally rapid with the patients supine. However, when the subjects were erect, the clearance rates were abnormally slow, with the lower zones showing much slower clearance than the upper zones. In two patients, there was evidence of gravitational mucus drainage into the lower zones (Fig. 2).

The patients with bronchiectasis did not show the distinct foci of radionuclide that were seen in the tracheas of normal subjects, either with the patients erect or supine, in spite of the very rapid clearance of particles from the lungs in the supine position.

DISCUSSION

Stewart (1948) and Hiding (1945) demonstrated the considerable forces of cilial action, so it is not surprising that muco-ciliary transport is unaffected by gravitational forces in healthy subjects. In patients

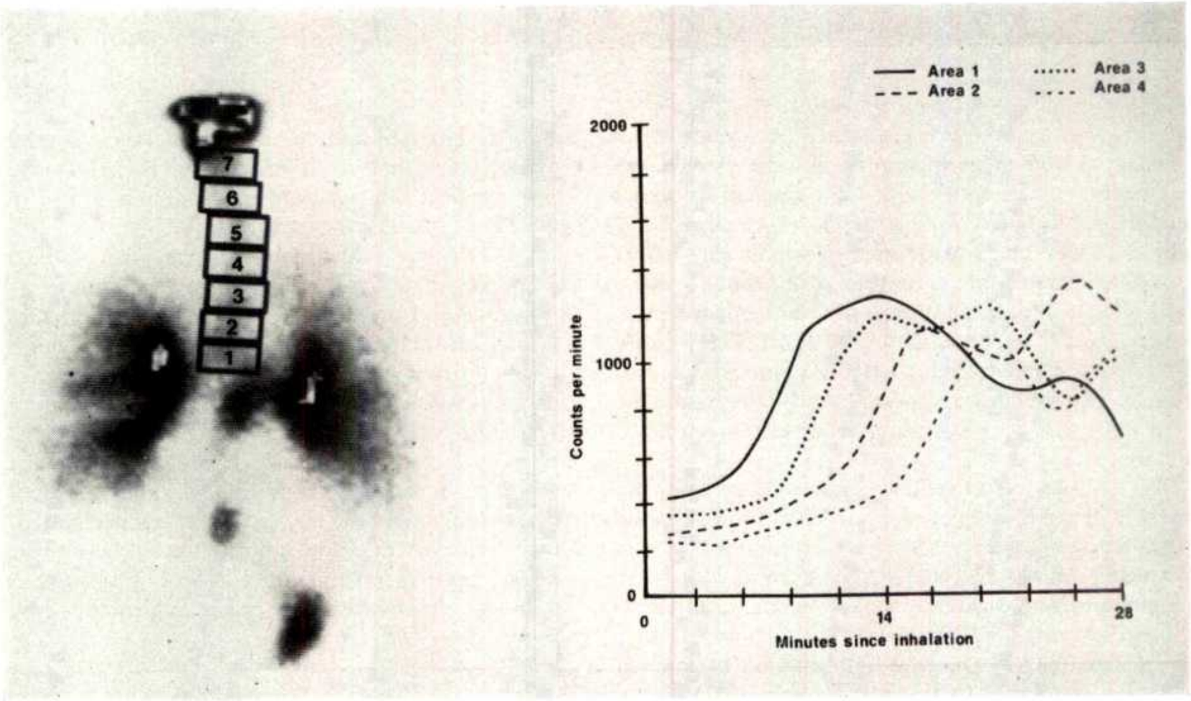

FIG. 1.

Placement of areas-of-interest along trachea and resulting counts/time curves tracing mucus movement.

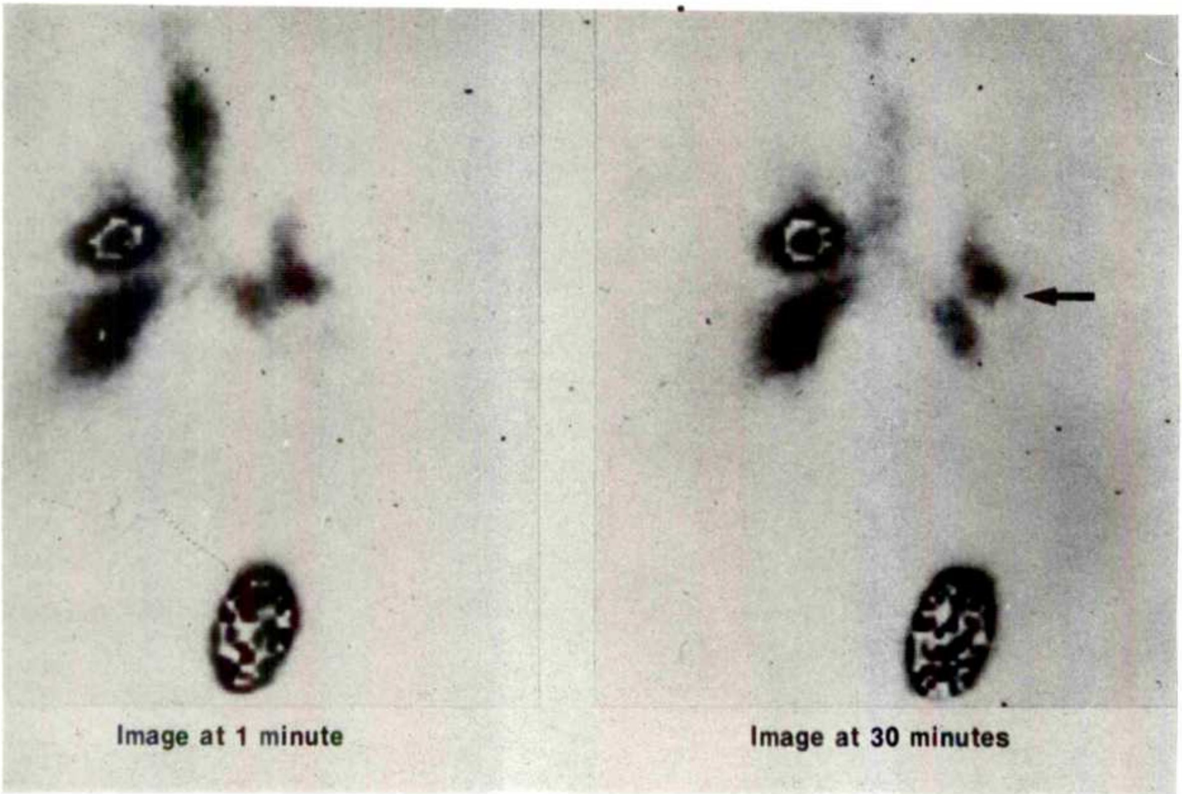

FIG. 2.

Anterior view of lungs in patient with bronchiectasis showing drainage of mucus into right lower lobe (arrow).

with bronchiectasis, however, there appears to be a marked dependance on posture. This may be due to ineffective cilial action, or alteration in mucosal quantity or viscosity. The rapid clearance of particles observed when these patients were supine may reflect the excessive production of mucus in bronchiectasis, and the prolonged clearance in the same patients when erect may be due to the increased burden placed on ciliary transport by gravitational effects on the excess mucus, compounded by the damaged mucous membrane resulting from chronic inflammation.

No distinct foci of radioactivity were noted in the trachea of the bronchiectatic subjects. Thus it seems that in these patients there is a continuous mucus "stream" in the trachea, rather than the discrete particles of mucus noted in healthy subjects, which further indicates that the inefficient transport is due, at least in part, to excessive production of mucus. This supports the findings of Irvani and Van As (1972).

It seems that this method could be used to monitor clinical progress of patients with bronchiectasis, and also to assist in the assessment of regions in the lungs where surgical intervention is considered, since, in some cases, mucus was observed to drain into regions of less-effective muco-ciliary transport, which thereby acted as foci for further inflammation.

The method described would appear to offer several advantages over most previously used methods of monitoring muco-ciliary transport since it is non-invasive, does not require any form of preparation of the patient, and uses particles of similar size to those normally deposited in the tracheo-bronchial tree. Simultaneous measurement of total or regional lung clearance and tracheal muco-ciliary transport rate appears practicable, and gives consistent results. The method is easily practised in the routine clinical situation and is well tolerated by patients.

ACKNOWLEDGMENTS

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Book review

Dickens's Doctors. By Sir David Waldron Smithers, 1979, pp. xiii + 111. (Pergamon Press, Oxford) £5·50/$15·00. ISBN 0-08-023386-4

This is an extremely enjoyable small book and one which I intend to give to friends whether they already know and enjoy Dickens' writings or not, because the success of Sir David's graceful writing is almost certain to make anyone an admirer of Dickens. My only regret about this elegant book is that it is not as long as I would wish it to be.

Dickens's Doctors is a scholarly anthology: the fictitious doctors have been set in cameos which are suitably in context and accompanied by comments of a sort that one doctor might make of another's manner and demeanour. Dickens' doctors have been chosen in chronological order and thus illustrate Dickens' development as a great writer.

The doctors whom Dickens met in real life, those who must have influenced him, are also described and their portraits often shown in black and white reproductions.

The present author is himself in part revealed for it is plain that he has an enormous regard for Dickens' writings which he must have read and re-read and thought about for years, while also reading widely about the circumstances of Dickens' life and the England of his day.

This charming volume has a bibliography and an index. There are ten portraits of doctors whom Dickens met, 19 contemporary illustrations from Dickens' books and a reproduction of a painting showing one of Sir Henry Thompson's Octave dinners, there being on this occasion ten seated, including Horsley, Spencer Wells, Lauder Brunton, James Paget and Richard Quain, the anatomist.

THELMA BATES.

1979, *British Journal of Radiology*, *52*, 972–977

Tumour regression during radiation treatment as a guide to prognosis

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ABSTRACT

The response to radiation treatment was studied in 110 patients with head and neck cancer with a minimum follow-up of two years. If the tumour had disappeared by the mid-point of treatment (3000 rad), a significantly more favourable prognosis was found in early ($T_{1-2}N_0$) tumours. On the other hand, whether these tumours had disappeared or were persisting at the end of treatment, there was no difference in the recurrence during the observation time of two years.

In advanced tumours there was no significant relationship between disappearance by the mid-point of treatment and recurrence up to two years. But when an advanced tumour had disappeared at the end of treatment, the prognosis was significantly more favourable. The unpredictability and often impossibility of judging the prognosis in individual cases encourages the authors to stress the importance of executing the original individual surgical plan irrespective of radiation response.

The regression rate of a tumour during radiation treatment has often been used as an indicator of radiocurability. Several authors (Marcial and Bosch, 1970; Lederman, 1972; Grossman *et al.*, 1973; Glucksmann *et al.*, 1967) have reported that the regression rate during irradiation predicts the control or failure of a human tumour treated with radiotherapy. According to Lederman (1972), the choice of surgical treatment or of continued radiotherapy for laryngeal tumours should be determined depending on the regression rate after 4000 rad of radiotherapy.

However, as the regression rate of a malignant tumour during irradiation depends on several different parameters, *e.g.* the amount of stroma and oedema in the malignant tissue, the growth rate of the tumour (Breur, 1966), and the ability of the vascular system to remove lysed tumour cells (Suit *et al.*, 1965), it may vary in different tumours independently of the final local cure of the disease.

With regard to animal experiments, Denekamp (1977) recently noted a distinct correlation between the regression of a mouse tumour and the radiocurability. On the other hand, Suit *et al.* (1965) and Trott *et al.* (1967) did not show any correlation between tumour shrinkage and radiocurability in animal experiments. Sobel *et al.* (1976) reported that a persistent human tumour at the end of radiotherapy of the head and neck area did not predict an eventual local failure. The same observation was reported by Suit *et al.* (1965) in their clinical studies.

For several decades, fast regression of the tumour during radiotherapy has maintained optimism in the clinician about the local radiocurability of a tumour. The present investigation of head and neck tumours was intended to shed light on this question.

The regression of the head and neck tumours treated at the Radiotherapy Departments of Middle Finland Central Hospital and Turku University Central Hospital was studied and correlated with the subsequent local cure or recurrence. At the same time correlation of the histological grade of the tumour with the regression rate was also investigated.

MATERIAL AND METHODS

The original series consisted of 123 patients with histologically verified head and neck epidermoid carcinomas treated with radiotherapy alone during the years 1968 to 1974. The site of the tumours is given in Table I. The staging of the cases according to the TNM classification (UICC 1968) is presented in Table II. Thirteen patients with advanced cancer died with distant metastases or intercurrent disease within two years without recurrence in the primary site or neck nodes and are excluded from the further analysis of the results, which thus concerns 110 patients.

Radiation treatment was delivered according to individual treatment plans with cobalt equipment using daily doses of 200 rad. The total tumour dose

TABLE I

SITE OF HEAD AND NECK CARCINOMAS TREATED WITH IRRADIATION

Larynx	84
Nasopharynx	5
Oropharynx	8
Hypopharynx	12
Oral cavity	14
Total	123

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was usually 5500 to 6500 rad in six to nine weeks. The mean dose was 5778 rad. At the mid-point of the treatment there was a pause of two to three weeks.

With the exception of the diagnostic biopsies, no other operative measures were performed. The patients were examined by an oto-laryngologist at intervals of two to four weeks during the treatment and of one to two months after irradiation. The regression of the tumour was evaluated in terms of decrease in the volume at the mid-point of the treatment, *i.e.* during the last days of the pause, and at the end of radiotherapy. The regression of the tumour was evaluated as follows:

(1) the tumour had disappeared,
(2) the tumour had diminished by more than 50% of its volume,
(3) the tumour had diminished by less than 50% of its volume,
(4) no change or further growth.

In some cases evaluation of the tumour size at the mid-point and at the end of radiotherapy was disturbed by radiation-induced oedema and there is some incomplete information for this reason.

Early and advanced tumours are considered separately. As larynx cancer deserves special interest, early laryngeal tumours are also presented separately. The observation time was at least two years.

TABLE II

TNM CLASSIFICATION OF HEAD AND NECK CARCINOMA

$T_1N_0M_0$	42
$T_2N_0M_0$	20
$T_3N_0M_0$	24
$T_4N_0M_0$	4
$T_1N_{1-2}M_0$	8
$T_2N_{1-2}M_0$	2
$T_3N_{1-2}M_0$	11
$T_4N_{1-2}M_0$	3
$T_{1-4}N_3$	8
$T_3N_0M_1$	1
Total	123

RESULTS

Evaluation of the results was made by chi-square test or, when necessary, by Fisher's exact method for 2×2 tables. When the probability fell to less than 0.05 the difference is said to be significant and exact p values are given in the tables.

All stages

The degree of diminution of the tumour at the mid-point of radiation treatment, *i.e.* at a dose of 3000 rad, is presented in relation to the final local result in Table III. Thirty-one per cent (8/26) of those whose tumour had disappeared during this initial period developed a recurrence. Sixty-four per cent (42/66) of the cases with a persisting tumour developed a recurrence. The difference in favour of early regression is statistically significant.

In Table IV diminution of the tumour at the end of the treatment is presented in relation to the final result. Forty-three per cent (33/77) of the tumours which had disappeared at the end of irradiation developed a recurrence within two years. Seventy per cent (19/27) of the tumours which persisted at the end of therapy developed recurrences. The difference in favour of regression at the end of treatment is statistically significant.

Early tumours

In Table V early tumours ($T_{1-2}N_0$) of the head

TABLE III

RECURRENCE OF HEAD AND NECK CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE MID-POINT OF RADIATION TREATMENT (ALL STAGES)

Tumour size at the mid-point of treatment		No recurrence within 2 years		Recurrence within 2 years	
Disappeared	(26)	18 (69%)		8 (31%)	
			$p = 0.009$		
Diminished by more than 50%	(39)	16 (44%)		22 (56%)	
Diminished by less than 50%	(20)	5	24 (36%)	15	42 (64%)
No change	(7)	2		5	
Incomplete information	(18)	11		7	
Total	(110)	53		57	

TABLE IV

RECURRENCE OF HEAD AND NECK CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE END OF RADIATION TREATMENT (ALL STAGES)

Tumour size at the end of treatment	No recurrence within 2 years			Recurrence within 2 years	
Disappeared	(77)	44	(57%)	33	(43%)
			$p=0.03$		
Diminished by more than 50%	(17)	6	8 (30%)	11	19 (70%)
Diminished by less than 50%	(8)	2		6	
No change	(2)	0		2	
Incomplete information	(6)	1		5	
Total	(110)	53		57	

TABLE V

RECURRENCE OF $T_{1-2}N_0$ HEAD AND NECK CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE MID-POINT OF RADIATION TREATMEHT

Tumour size at the mid-point of treatment	No recurrence within 2 years			Recurrence within 2 years	
Disappeared	(17)	14	(82%)	3	(18%)
			$p=0.02$		
Diminished by more than 50%	(22)	12	15 (50%)	10	15 (50%)
Diminished by less than 50%	(4)	2		2	
No change	(4)	1		3	
Incomplete information	(14)	10		4	
Total	(61)	39		22	

and neck are presented. Eighteen per cent (3/17) of the tumours which had disappeared by the mid-point of radiation treatment developed a recurrent tumour within two years while 50% (15/30) of the cases with a persistent tumour developed a recurrence. This difference is statistically significant.

At the end of treatment (Table VI) 49 tumours were non-detectable, 35% (17) of them having a recurrence later on. Of the nine tumours still present three developed a recurrent tumour.

TABLE VI

RECURRENCE OF $T_{1-2}N_0$ HEAD AND NECK CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE END OF TREATMENT

Tumour size at the end of treatment	No recurrence within 2 years			Recurrence within 2 years	
Disappeared	(49)	32	(65%)	17	(35%)
			$p=0.8$		
Diminished by more than 50%	(8)	6	6 (67%)	2	3 (33%)
Diminished by less than 50%	(–)	–		–	
No change	(1)	0		1	
Incomplete information	(3)	1		2	
Total	(61)	39		22	

TABLE VII

RECURRENCE OF $T_{1-2}N_{1-3}$ AND $T_{3-4}N_{0-4}$ HEAD AND NECK CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE MID-POINT OF TREATMENT

Tumour size at the mid-point of treatment	No recurrence within 2 years			Recurrence within 2 years	
Disappeared	(9)	4	(44%)	5	(56%)
			$p=0.18$		
Diminished by more than 50%	(17)	5	9 (24%)	12	28 (76%)
Diminished by less than 50%	(16)	3		13	
No change	(4)	1		3	
Incomplete information	(3)	1		2	
Total	(49)	14		35	

Advanced tumours

Of the 49 advanced tumours ($T_{1-2}N_{1-3}$ and $T_{3-4}N_{0-3}M_{0-1}$) only nine disappeared by the mid-point of the treatment; 56% (5/9) of them developed a recurrence within two years (Table VII). Seventy-six per cent (28/37) of the persisting tumours developed a recurrence later on. The seemingly more favourable prognosis with early disappearance is not statistically significant.

When the advanced tumours are considered at the end of the treatment (Table VIII), it appears that 57% (16/28) of the tumours which had disappeared

TABLE VIII

RECURRENCE OF $T_{1-2}N_{1-3}$ and $T_{3-4}N_{0-3}$ HEAD AND NECK CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE END OF TREATMENT

Tumour size at the end of treatment	No recurrence within 2 years	Recurrence within 2 years
Disappeared	(28) 12 (43%)	16 (57%)
	$p = 0.02$	
Diminished by more than 50%	(9) –	9
Diminished by less than 50%	(8) 2 } 2	6 } 16 (89%)
No change	(1) –	1
Incomplete information	(3) —	3
Total	(49) 14	35

TABLE IX

RECURRENCE OF T_1N_0 LARYNX CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE MID-POINT OF TREATMENT

Tumour size at the mid-point of treatment	No recurrence within 2 years	Recurrence within 2 years
Disappeared	(13) 13	–
	$p = 0.04$	
Diminished by more than 50%	(10) 5	5
Diminished by less than 50%	(3) 2 } 7 (50%)	1 } 7 (50%)
No change	(1) –	1
Incomplete information	(9) 6	3
Total	(36) 26	10

TABLE X

RECURRENCE OF T_1N_0 LARYNX CARCINOMA IN RELATION TO TUMOUR REGRESSION AT THE END OF TREATMENT

Tumour size at the end of treatment	No recurrence within 2 years	Recurrence within 2 years
Disappeared	(30) 22 (73%)	8 (27%)
Diminished by more than 50%	(4) 3	1
Diminished by less than 50%	(–) – } 3	– } 2
No change	(1) –	1
Incomplete Information	(1) 1	–
Total	(36) 26	10

TABLE XI

RECURRENCE OF HEAD AND NECK CARCINOMA IN RELATION TO THE HISTOLOGICAL DIFFERENTIATION (ALL STAGES)

Grade of Differentiation		No recurrence within 2 years	Recurrence within 2 years
Well	(51)	24	27
Moderately	(37)	20	17
Poorly	(16)	6	10
Total	(104)	50	54

developed a recurrence within two years. Eighty-nine per cent (16/18) of the cases with tumour persisting at the end of therapy developed a recurrent tumour. The better prognosis in cases with disappearance is statistically significant.

Larynx cancer

Early larynx carcinomas (T_1N_0 and T_2N_0) are reviewed separately. All thirteen T_1N_0 carcinomas which had disappeared by the mid-point of the treatment remained cured (Table IX). Fifty per cent (7/14) of the cases with persistent tumour at the mid-point of the therapy had a recurrence within two years. This difference is statistically significant.

Twenty-seven per cent (8/30) of the carcinomas which had disappeared at the end of radiation treatment developed a recurrence; of the five persisting tumours, two recurred (Table X).

No statistically significant differences were found between tumours which disappeared (3) or persisted (7) at the mid-point of therapy among the 12 somewhat larger (T_2N_0) laryngeal carcinomas. In two cases the information about the tumour at the mid-point of therapy was incomplete. No statistical significance was demonstrated even in the 12 T_2N_0 tumours which disappeared (11) or persisted (1) at the end of therapy.

Different grades of regression

A statistical analysis after regrouping the cases according to the degree of regression did not reveal any different characteristics to those found on the basis of complete disappearance compared with all degrees of persistence.

Correlation of histological differentiation with tumour recurrence and regression

The possible correlation between the histological grade and radiocurability in cases with sufficient information is considered in Table XI. There was no statistically significant difference between well, moderately and poorly differentiated tumours in relation to recurrence, nor when the material was separately studied for the early ($T_{1-2}N_0$) (57 cases) and advanced ($T_{1-2}N_{1-3}$, $T_{3-4}N_{0-3}M_{0-1}$) tumours (47 cases).

The histological differentiation did not correlate with the tumour regression either in the middle or at the end of radiation therapy.

DISCUSSION

A series of 110 head and neck cancer patients treated with radiotherapy is reported. The minimum follow-up observation of two years may give a reasonable indication of the permanent result.

Observations made at the mid-point of radiation treatment

A statistically significant ($p=0.009$) correlation was observed between fast regression, *i.e.* disappearance of the clinically recognizable tumour, and freedom from a recurrence for at least two years. A closer study of the cases makes this observation valid for early tumours ($T_{1-2}N_0$), but is statistically insignificant for advanced tumours. We recommend that the original surgical plan should remain unchanged even after a complete response to radiation, because the prognosis for advanced tumours is not significantly improved (Table VII) and a considerable risk (18%) of recurrence prevails even for early tumours. Early (T_1N_0) laryngeal carcinomas in which a complete regression has occurred by the mid-point of treatment are an exception, seeming to have a good prognosis. This series also supports the use of radiation as the primary therapy of early laryngeal cancer. Our recommendation thus conflicts with Lederman's (1972), but is in accordance with the report of Sobel *et al.* (1976) who likewise did not find any correlation between the radiation response at the mid-point of the therapy and cure for advanced tumours.

Observations at the end of radiation

As expected, a greater incidence of failures appeared among cases in which the tumour persisted at the end of radiation than in cases in which it had disappeared (Table IV). A closer study shows that the difference concerns only advanced tumours but not the early (T_{1-2}) ones. The lack of effect of the size of the tumour on radiation response was demonstrated in studies of Suit *et al.* (1965), Fazekas *et al.* (1972) and Sobel *et al.* (1976).

In animal experiments regression has been shown to correlate with the size of the tumour when small (Denekamp, 1977). Similarly, a larger dose of radiation was required in large tumours to cause the same effect as in small tumours. This observation by Schaeffer *et al.* (1977) was explained by different oxygenation of the tumour tissue in tumours of different sizes. Our observations, especially for the advanced tumours, may only be the consequence of the greater mass of the tumour. Early tumours may be completely absorbed during the first half of the radiation therapy while the more advanced ones require a longer time even when there is a favourable response.

The great variation in the speed of regression may be reflected by the finding that 25% (27/101) of tumours of this series persisted at the end of treatment, but 30% (8/27) of them disappeared subsequently and were registered as cures after two years. On the other hand, 43% (33/77) of the tumours which had disappeared at the end of treatment recurred. Olofsson and van Nostrand (1973) and Kortekangas *et al.* (1977) reported that tumour cells may be detected histologically in the operative specimen after irradiation in spite of the fact that the tumour was no longer clinically detectable. Also the opposite finding (*e.g.* Kortekangas *et al.*, 1977), a clinically persisting tumour but no neoplastic cells on histological examination, reflects the difficulty and uncertainty of clinical judgement of persistence or disappearance.

Correlation of histology and radiation response

In the present series there was no correlation between the histological grading and subsequent cure of the tumour, nor even any correlation between differentiation and speed of regression. The paper of Marcial and Bosch (1970) concerning cervix carcinoma reported the same finding. Thus too much attention should not be given to the grade of differentiation when planning either operative or continued irradiation treatment.

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Book reviews

The Toxicity of Plutonium, Americium and Curium. By J. C. Nenot and J. W. Stather, pp. xii+225, 1979 (Pergamon Press Ltd., Oxford), $27.50/£14.
ISBN 0-08-023440-2.

This book is a report prepared under contract for the Commission of the European Communities within its research and development programme on "plutonium recycling in light water reactors". Its object is to provide a biological basis for an assessment of the radiological health problems resulting from human exposure to plutonium, americium and curium.

For the most part these requirements are met in ten chapters. The authors properly identify the dearth of reliable human experience and the difficulties of extrapolating from animals to man as major problems and also show that most information coming from research effort is concerned not unexpectedly with plutonium. Their choice of subject material accurately reflects majority opinion on the most fruitful overall research method, enabling them, in their penultimate chapter, to come to "a quantitative assessment of the biological consequences of human exposure to plutonium, americium and curium".

There is, however, some unevenness of presentation. The assistance which the authors acknowledge in preparing or revising three of the chapters no doubt led to differences in writing style but may also have contributed to avoidable repetition. This is especially true in the discussions about nuclides in lymph nodes where some inconsistency is also seen.

There is no doubt that in this very active field it is necesdary frequently to update available information under one cover. In that sense this book is timely and much of the bibliography is recent (34% is post 1974 with less than half of this from the laboratories of the authors). However, there are some gaps and several references are misquoted in the text. In addition some conclusions are drawn which appear to need the support of published work.

In short, a careful reader can use this book profitably to help him to understand the direction of most of the research effort in the field. The bibliography is moderately extensive and should provide a valuable basis for further reading.

E. R. Humphreys.

Instrumentation and Monitoring Methods for Radiation Protection, NCRP Report 57, pp. v+177, 1978 (*NCRP Publications, Washington, D.C.*), $5.00.
ISBN 0-913392-40-5.

This report, which has been in the course of preparation since the early 1960's, supersedes NCRP Report 10 which was published as National Bureau of Standards Handbook 51 in 1952.

Two short introductory chapters are followed by one on area survey methods, the longest in the report. This considers not only monitoring as such but also includes lengthy check lists of all factors that should be considered in a radiation protection survey. It then goes on to make recommendations for specific types of installations, ranging from medical, dental and industrial radiography, through X rays from electronic equipment such as television receivers, through high-energy accelerators, sealed and unsealed radioactive sources, on to reactors and critical facilities. A chapter on personnel monitoring methods covers both external and internal monitoring and the investigation of unusual exposures, and ends with a long list of the information to be included on personal dose records.

The subject of instrumentation is eventually reached half way through the report which attempts to cover all types of radiation detector and measuring instrument for all types of radiation, both external and internal, for all types of purpose, in just 27 pages. Such condensation inevitably leaves no room for explanations and, equally inevitably, leads to short, packaged statements that give a false impression or are only half-truths. The reader familiar with instrumentation will find several examples without difficulty.

The report ends with a brief account of the procedures and measurements required for dealing with accident situations.

It is difficult at decide at what readership the report is aimed. In fairness to the authors, it is a conscientious attempt at the impossible task of covering both the principles of radiation protection procedures and the detailed performance considerations of the instruments used in radiation monitoring, all in a single report.

D. F. White.

1979, *British Journal of Radiology*, *52*, 978–983

Treatment time and sub-lethal repair in radiotherapy

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ABSTRACT

The repair of sub-lethal damage is now universally accepted by radiotherapists and its role in fractionated radiotherapy fully appreciated. However, it may also influence the survival of cells during a single daily treatment—a phenomenon not always considered.

Chinese hamster ovary cells have been irradiated with total doses of 750 rad or 500 rad under optimum growth conditions and the effect of repair of sub-lethal damage on survival examined for a split dose given with 30 minutes separation. Our results show that repair of sub-lethal damage is a very rapid process and the recovery ratio, *i.e.* the increase in survival when the radiation dose is delivered in two or more parts, is approximately one per cent per minute. The results show quite clearly that both dose-rate and the total time for a daily treatment may significantly change the number of survivors following radiation.

Using a carefully designed irradiation set up to achieve accurate dosimetry, and many replicate cell samples, it has been demonstrated that the recovery ratio is greater than 1.2 for time intervals of 30 minutes whether the radiation is given in two equal parts or five portions. The statistical significance of the data was extremely good with the "p" value never worse than 0.01.

Using these results we have examined the effect that changing a patient's treatment from a high dose-rate linear accelerator to a low dose-rate telecobalt unit might have on cure rates.

This analysis suggests that doses should be increased for long daily treatment times and that care must be exercised when high-energy machines with different dose rates are used in multi-centre trials.

Elkind and Sutton (1960) demonstrated that sub-lethal repair for mammalian cells in tissue culture was considerable if several hours elapsed between two doses of radiation. Although radiotherapists had realized for many years that increasing the number of fractions raised the total dose that could be given to a tumour, these studies were the first clear demonstration of sub-lethal recovery or repair in mammalian cells. Elkind and Whitmore (1967) have listed numerous examples of sub-lethal repair in many different biological systems, and Winans *et al.* (1972) showed that repair can be a very rapid process with half the maximum repair taking as little as 20 minutes in their cultured mammalian cell system. Repair can result in an increase in survival by a factor of 1.5 to 100 depending on the cell line and experimental set-up, and it usually reaches its first peak at a split-dose interval of between 1½ and 3 h.

Most estimates of sub-lethal repair have used time intervals greater than 30 minutes between split doses and it is difficult to ascertain the initial shape of the repair curve from these experiments. Repair is a rapid process (Winans *et al.*, 1972) and therefore must be affected by dose-rate. Fu *et al.* (1975), using a continuously irradiated *in vivo* EMT6 tumour, a gut clone assay, and a bone marrow CFU assay, all in the mouse, showed that for a decrease in dose rate from 270 to 36 rad per minute repair increased survival by a factor of 2.3. Close examination of the classical *in vitro* dose-rate studies of Hall (1972) shows that even in these experiments the repair ratio increased to 1.05 as the dose rate dropped from 200 to 40 rad per minute. A repair ratio of only 1.05 may seem insignificant, but if it is the number of cells killed in a tumour that finally determines whether there is a local recurrence or not such small differences may be all too significant.

We therefore decided to examine the repair of sub-lethal damage which occurs during the time taken for a multi-field fractionated treatment, to see if this is dependent on dose rate or the length of the daily treatment time. By choosing a cell line with a large extrapolation number it might be possible to prove a dependence on dose rate even for fractionated doses which differ by only a few minutes, but such a cell line might exaggerate what happens in the patient. Therefore we used a Chinese hamster ovary cell line maintained in this laboratory for many years and known to have a split-dose recovery ratio of about 2.0. We have examined the recovery ratio (the number of survivors after a split dose divided by the number after a single dose) using times and doses as close to conventional radiotherapy regimes as possible, with the mammalian cells kept at optimum growth conditions during radiation treatment and recovery.

MATERIALS AND METHODS

Chinese hamster ovary K1 cells were routinely cultured in F10 medium supplemented with 10% fetal calf serum. Sub-culturing was carried out every four days and the generation time for this cell line was 12 to 14 h. For the radiation experiments a monolayer culture was harvested with D_2 trypsin (Paul, 1965) and the resulting single cell suspension was added to 5 cm polystyrene Petri dishes. The volume of medium in each dish was 4 ml and the number of cells was approximately 500. The plating efficiency was about 70%. The Petri dishes were incubated overnight at 37°C in 95% air: 5% CO_2 to allow attachment and to remove any perturbations that might result from the handling procedure, *i.e.* to establish a normal growth pattern.

The Petri dishes were transferred to a portable incubator at 37°C with an atmosphere of 95% air: 5% CO_2 approximately 2 h before irradiation. These optimum growth conditions were maintained throughout irradiation and for at least 1 h afterwards; then the Petri dishes were transferred back to the original air:CO_2 incubator for a further five to seven days. Resulting colonies were fixed with formol saline stained with crystal violet and colonies of 50 cells or more were counted. Such colonies are deemed to have resulted from a cell that had survived the irradiation. The Petri dishes in the portable incubator were irradiated at two dose levels, nominally 750 rad and 500 rad. No attempt was made to produce complete survival curves so the Petri dishes which could be accommodated in the small portable incubator were concentrated at these two dose levels to ensure statistically significant results. A survival curve produced separately and typical of the cell response is shown in Fig. 1. It has a D_0 of 290 rad and an extrapolation number of 2.6 after correction for multiplicity of 1.6.

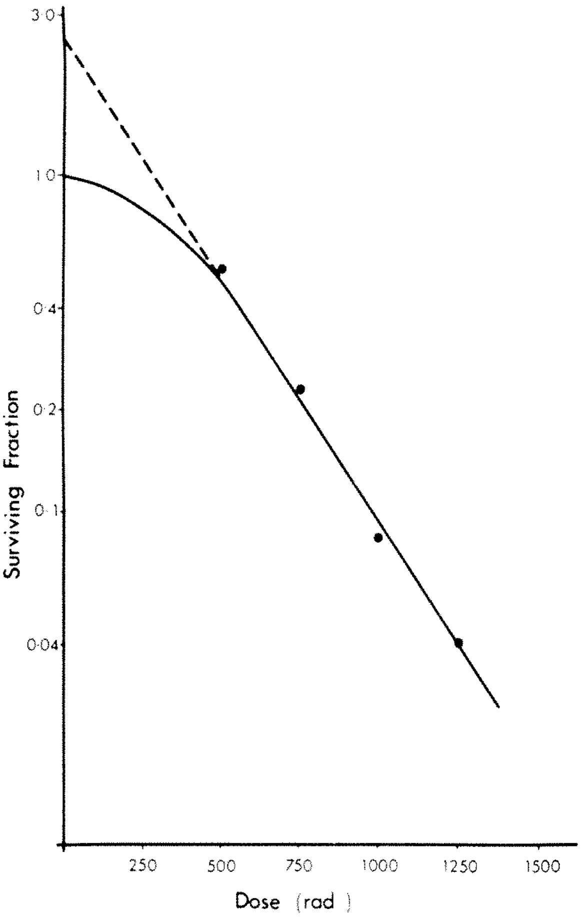

FIG. 1.

A typical survival curve for the cell line used.

Dosimetry

It was decided to keep all the cells for both split and single dose experiments in the same environment to prevent differences in handling procedures from affecting the results. Thus the cells were irradiated on a Gammatron telecobalt unit in a portable incubator, with one half shielded at a time. To reduce scatter and stray radiation we supplemented the trimmers of the Gammatron with an extra sheet of lead 2 cm thick placed over half the incubator and we relied on this reduction in the penumbra to shield the single-dose dishes when the second half of the split dose was given to the other half of the incubator. Dose rates in the dishes were measured with a disc-shaped thin-window ionization chamber of depth 2 mm which fitted snugly into the bottom of a dish from which the base had been removed. It was calibrated against the known output under normal conditions. Under these conditions dose distributions plotted at the level of the cells with similar build-up showed the dose in the penumbra to be about 2% of that in the main beam. Within the beam the range of doses at the dishes was ±4% for the 40×40 cm field and ±1% for the 15×40 cm field. These variations affected the split and single doses equally. To increase the number of dishes in each sample they were stacked in pairs. The dose received by the bottom dish of each pair was 98% of the top one. Thus the total standard deviation of the doses was ±2%. The dose received in the penumbra was minimized by giving half the total dose with the larger field, without any extra lead. This necessitated a small time interval half-way through the single dose of about one minute during which the field size was increased from 15×40 cm to 40×40 cm, the lead shield removed and the beam recentred. Thus the cells given split doses received irradiation in three parts, *i.e.* 49% at the start followed by 1% when the first part of the single dose was being given and finally 50% at the end. The cells given single doses also received irradiation in two parts, *i.e.* 1% during the first half of the split dose and 99% at the end. This arrangement is shown diagrammatically in Fig. 2 for a split-dose interval of 30 minutes. The mean dose rates for both fields were equal at approximately 100 rad per minute. The single dose was given at the end of the experiment to ensure that any increase in multiplicity would increase the number of survivors and hence decrease the difference that may be caused by repair of sub-lethal damage due to splitting the dose. The increase in multiplicity for this cell line with a doubling time of about 14 h is estimated to be only 1.5% over the 13 minutes separating the mid-points of the split and single doses in Fig. 2. The main dose level investigated was 750 rad to the upper shelf in the portable incubator. The lower shelf received the dose of 500 rad but this included a larger scatter component.

RESULTS

The results of the three main experiments are shown in Table I. The standard deviations shown are best estimates as the colony counts from some experiments had standard deviations less than that required from Poisson distribution. This is to be expected, but such low standard deviations should not be used to calculate the statistical significance of the result (Boag, 1975). Therefore a best estimate for each set of data was calculated assuming at least a Poisson variance plus the mean of the residual variances obtained for these three experiments (A, B and C, Table I) and three other experiments. The additional three experiments were not included in Table I because optimum growth conditions were not achieved, *i.e.* incubation was between 30 and 35°C. These best estimates were used to calculate the standard error of the ratio and the "t" value; the probability "p" was then read from the appropriate tables. Without this variance correction the "p" values were 0.006, 0.00002 and 0.00001 respectively.

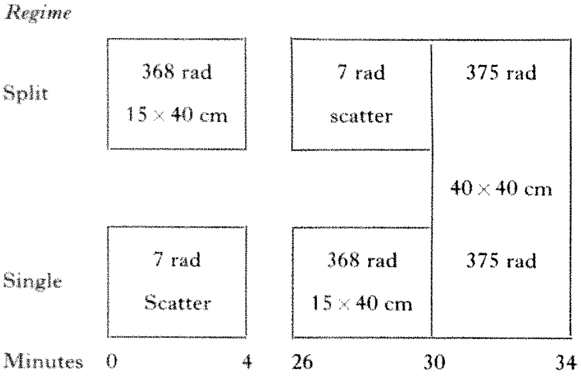

FIG. 2.
Times of Irradiation.

The three experiments conducted at a sub-optimum incubation temperature showed no obvious differences between their variances and those in Table I nor between the single and split doses. The average values of R (recovery ratio), t, degrees of freedom, and p for these three experiments were 1.22±0.06, 4, 25, and 0.001 respectively.

The results in Table I show a very significant difference between survival after single and split irradiations for the three regimes tested, *i.e.* 30 min gap, 15 min gap and five doses spread equally over 30 min with each irradiation lasting 1.5 min. The mean surviving fractions after a dose of 750 rad were 0.30 for single doses and 0.37 for split doses. Fewer Petri dishes were used for doses of 500 rad and as there was more scattered radiation a comparison was expected to be more difficult. However, the results shown in Table II again demonstrate a significant difference in survival between the single and split doses. The mean surviving fractions were 0.53 for single doses and 0.60 for split doses.

A further experiment with the shelf of the portable incubator modified into six compartments with lead sides was performed to obtain an indication of the

TABLE I

COLONY COUNTS AT 750 RAD (500 CELLS PER DISH)

Experiment	Single dose			Split dose			Ratio (R) ± SE	t	p
	No. dishes	Mean no. colonies	Standard deviation σ	No. dishes	Mean no. colonies	Standard deviation σ			
A	16	126.5	17.0	16	155.7	17.8	1.23±0.05	4.7	0.0002
B	15	80.5	15.6	14	98.9	16.2	1.23±0.08	3.1	0.005
C	16	117.8	16.8	16	152.3	17.8	1.29±0.06	5.7	0.00001

A = 2 × 375 with 30 min gap; B = 2 × 375 with 15 min gap; C = 5 × 150 over 30 min. The mean number of colonies on the control dishes was 360, with a multiplicity of 1.6.

TABLE II

Colony counts at 500 rad (500 cells per dish)

Experiment	Single dose			Split dose			Ratio (R) ± SE	t	p
	No. dishes	Mean no. colonies	Standard deviation σ	No. dishes	Mean no. colonies	Standard deviation σ			
A	11	158.3	26.1	12	188.6	22.8	1.19 ± 0.07	3.0	0.007
B	5	158.4	6.3	6	174.2	20.4	1.10 ± 0.06	1.7	0.13
C	11	193.1	13.4	12	217.3	15.9	1.13 ± 0.03	4.0	0.0007

Note: standard deviations are not best estimates. A = 2 × 250 with 30 min gap; B = 2 × 250 with 15 min gap; C = 5 × 100 over 30 min.

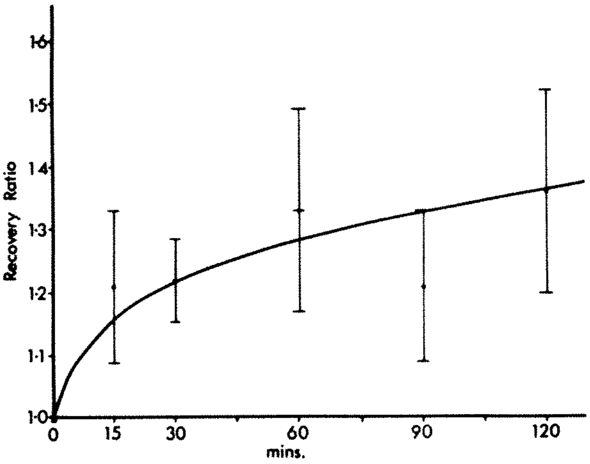

Fig. 3.

Changes in the recovery ratio of Chinese hamster ovary cells for split doses given 15 to 120 minutes apart.

change in the recovery ratio over two hours. The extra lead shielding of the Gammatron was as previously described. The results for a split dose of 375 plus 375 rad combined with those already mentioned in Table I are shown in Fig. 3. The error bars are the 95% confidence limits on the means of the recovery ratios obtained. It can be seen from this graph that there is probably a fast initial rise in recovery without any apparent delay after the irradiation. It must be noted that the time values on Fig. 3 and in Tables I and II relate to the intervals defined from centre to centre of the split doses so that the actual non-irradiation times (except for the small contribution by scatter) between the doses are four minutes less than those plotted. All the data show quite conclusively that the rate of recovery is probably greater than 1% per minute even for these Chinese hamster cells which have a maximum recovery ratio as low as 2.0. Throughout, no correction has been made to reduce the standard deviations by that due to the variation in dose over the Petri dishes nor to increase the differences in survival by adjustment for multiplicity. If these corrections were made they would have increased further the significance of the results.

Discussion

This rapid onset of repair of sub-lethal damage leads us to speculate about its effect during conventional radiotherapy treatments. The shortest time interval attempted in our experiments was 15 minutes; although this may be considered long for a radiotherapy treatment, the results obtained consistently pointed to a recovery ratio of approximately 1% per minute for time intervals of less than 15 minutes. The similar results obtained with the large intervals and the four smaller intervals (five doses) suggest that the important time factor in these studies is not the size of the gap but the overall time of irradiation. In radiotherapy treatments this will depend on setting up times, number of fields and dose rate.

The doses used may seem large but these must be assessed relative to the radiosensitivity of the cell line being used, and in this case the D_0 was high at about 300 rad. The surviving fractions are a better guide to the suitability of the doses. Thus a surviving fraction equal to 0.30 (at 750 rad) would be reduced to 10^{-8} by 15 treatments; for a surviving fraction of 0.53 (500 rad) 29 treatments would be required. This makes these survival levels ideal to represent conventional radiotherapy since treatment is given in 15 to 30 fractions by most radiotherapists.

The daily treatment time on a radiotherapy machine will be influenced by many factors including the following: (a) FSD. This will vary from machine to machine and will, depending on the

TABLE III

Total dose 5000 rad in 15 fractions, 330 rad per fraction

Machine	1st field	Setting up	2nd field	Setting up	3rd field	Total time	Recovery time
Linear accelerator	1 min.	5 min.	1 min.	5 min.	1 min.	13 min.	12 min.
Telecobalt	7 min.	5 min.	7 min.	5 min.	7 min.	31 min.	24 min.

Additional time on Telecobalt of 12 minutes produces a recovery ratio of 1.12.

method of treatment, probably be between 60 and 140 cm for high-energy machines. (b) Dose rate. Dose rates for high energy sources in most radiotherapy centres will be approximately 100 rad/min, but in a centre with a linear accelerator the dose rate may be nearer 300 rad/min. Telecobalt machines will have a continually decreasing dose rate which may be 100 rad/min when installed but falling to 50 rad/min before the source is changed. (c) Complexity of setup. The same site treated by different plans can require between two and five fields. Some patients who are very ill or frightened may pose a problem for the radiographer. Where this is combined with a multi-field set up, treatment can take a very long time. (d) Number of patients. This may well affect the speed of set-up since a large number will speed up throughput whereas a small number will give the radiographer more chance to be sympathetic and encouraging to frightened patients.

These four points are certain to operate at some time in a large radiotherapy centre and each will in its way change the overall treatment time. The response of a tumour is dependent both on tumour-cell survival and on tumour-cell kinetics, *e.g.* growth fraction which has been shown to vary between 30 and 80% and cell-loss factor which can vary greatly from 0 to 90% (Hall, 1972). Although the effects of hypoxic cells, cell reassortment around the cell cycle and inherent differences of sensitivity may affect the response within a tumour as a course of treatment proceeds, the recovery during a treatment session of cells within the growth fraction will still probably continue at a similar rate. It is the potentially dividing cells that are responsible for a local recurrence of tumour when therapy has been unsuccessful. The growth fractions in animal tumours seem to be remarkably constant even though the tumours may vary in histological type and degree of differentiation. Thus, in order to simplify further analysis, we have assumed that a tumour has 10^8 cells in the growth fraction, which is not unreasonable for a small tumour, and that its response to radiation can be characterized by a multi-target survival curve with constant sensitivity and extrapolation number.

If a treatment regime of 5000 rad is given in 15 fractions the treatment may be planned for any one of several treatment machines in a large radiotherapy centre. Let us consider two extremes, *e.g.* a linear accelerator with a dose rate of approximately 300 rad/min and a telecobalt unit at 50 rad/min. If there is a three-field treatment plan and the setting-up time is similar on both machines, *i.e.* 5 min per field, then Table III shows a plan of each treatment if the given dose is 300 rad/per field on the linear accelerator and 350 rad/per field on the telecobalt unit. The total treatment times vary by a factor of two and the estimate of recovery time comparable with the analysis of our experiments is the interval between the mid-points of the first and last fields. This will give an extra recovery time on the telecobalt unit of 12 min and hence a recovery ratio of 1.12, operating on each daily treatment. These treatments are repeated 15 times which gives a final recovery ratio on the telecobalt unit of $(1.12)^{15}=5.5$. This treatment regime might produce an 80% cure rate when used with the linear accelerator. Assuming a Poisson type distribution of surviving cells between patients this is equivalent to 0.22 cells remaining viable in the average patient, if patients with no cells are cured and those with one cell or more have a recurrence. However, repair of sub-lethal damage for tumours treated on the telecobalt unit would increase the average number of viable cells to $5.5\times0.22=1.21$. Patients with no viable cells are still cured but because the average number of cells per patient has been increased to 1.21 only 30% of the patients treated have now had their viable tumour cell number reduced to zero and can be said to be cured. A recovery ratio of 1.12 corresponding to a time difference of 12 minutes may seem too much. A difference of only five minutes (recovery ratio $=1.05$) would lead to a 63% cure rate. Assuming an extrapolation number of 2 and a D_0 of 177 rad (for convenience) for a tumour, the dose per fraction required to offset this 5% recovery at the 0.54 level of cell survival is 11 rad in a daily dose of 200 rad. This amounts to 330 rad in a total dose of 6000 rad which is considerable. In our opinion the literature cited earlier suggest that these calculations have underestimated the recovery so that an effect greater than 5% might be present.

It is interesting to note that a recovery factor of only 1.05 per fraction and an 80% cure rate could be sufficient for a significantly lower cure-rate to be produced in a well-matched series as small as 140 patients. It is hoped that some radiotherapists may find it interesting to carry out a retrospective analysis of clinical data where a change of therapy machines or of source in a telecobalt unit has occurred. It is hoped that research workers working with solid tumours in small animals may find these results and hypothesis worthy of testing in an *in vivo* system; or perhaps the data already exist and only a detailed analysis is required. However, a cautionary note is necessary regarding matching since a small difference in dose and/or tumour volume could mask the difference.

Our results suggest three important questions:

1. Should tumour doses be modified to allow for dose-rate differences between 50 and 300 rad/min?
2. Should tumour doses be modified to allow for very complex set-ups, *i.e.* the overall daily treatment time?
3. What is the correct allowance per minute of total treatment time?

It is important that these questions should be considered when treating under differing conditions and when setting up trials which might use different treatment machines. The experiments and calculations presented obviously simplify the true situation but nevertheless indicate that patients treated at a higher dose-rate should have a better chance of cure, all other factors remaining equal. The choice of the treatment machine should not affect the chance of cure.

ACKNOWLEDGMENTS

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Book review

Internal Radiation Dose in Diagnostic Nuclear Medicine. By H. D. Roedler, A. Kaul, and G. J. Hine, pp. 111, 1978 (Verlag Hildegard Hoffmann, Berlin), $16.50.
ISBN 3-873-44049-0

This small volume is intended as a pocket reference book for the absorbed radiation dose from radiopharmaceuticals commonly used in nuclear medicine diagnosis. It consists of a set of tables listing the doses to critical and investigated organs and to gonads and bone marrow. The tables are given in the new SI Units (grays and becquerels) as well as in non-SI Units (rads and curies). The tables are divided into groups relating to various physiological systems, each preceded by a thumb-nail sketch of the indications, principles of imaging, problems and techniques.

The small pocketable format suggests that it is intended to be a ready reference. The dosimetric tables are of some value but contain detailed information on more radiopharmaceuticals than one would need to have readily available and yet there is insufficient information to replace the standard reference works. The potted nuclear medical methodology sections are much too brief to be of any real value.

Overall this is not a very useful volume.

DAVID O. COSGROVE.

1979, *British Journal of Radiology*, 52, 984–988

Technical note

A multi-channel system for microwave heating of tissues

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Although recent research and experience have shown that hyperthermia administered alone, or in combination with ionizing radiations or drugs, may be useful in the treatment of cancer, there are many questions to be answered if such therapy is to be optimized. Many studies with experimental animals have been made using water-bath heating because of its simplicity. However, recent reports (Hume *et al.*, 1979a; Robinson *et al.*, 1978) indicate that temperature distributions in tissues heated in this way may be markedly affected by blood flow. Heating methods in which energy may be deposited at depth in tissues may produce more uniform temperature distributions than can be obtained by immersing tissues in hot water. Since the effects of hyperthermia are very strongly dependent on temperature, the development of methods to heat tissues uniformly is an important requirement both experimentally and clinically. Expertise acquired during the development of microwave heating techniques should prove particularly valuable since this means of inducing hyperthermia has been chosen in a number of clinical trials currently underway.

In the present report a microwave heating system which allows four volumes of tissue to be treated simultaneously is described. It is particularly useful in experiments involving rodents. The temperature in each field may be monitored and individually controlled. Because the size and shape of rodents can be characterized by dimensions which are comparable to the wavelength of microwaves at the frequencies allocated for medical purposes (2450 MHz and 915 MHz), the microwave absorption cross sections of these animals are strongly dependent upon orientation and changes in size and shape. To circumvent these problems tissue-equivalent phantoms have been developed (*e.g.* Cheung and Harrison, 1978; Hand *et al.*, 1979a) and used to transform the irregular geometry of the rodent to a simpler form. In the present system the part of the animal to be treated is immersed in physiologically-compatible liquid bolus and subjected to microwaves from parallel-opposed waveguide applicators.

MATERIALS AND METHODS

General description of heating system

Each of the animals to be heated is placed at one of four locations in a Perspex bath in which the liquid bolus is stirred and circulated. Bolus temperature is maintained a few tenths of a degree Celsius below the desired tissue temperature by continuously operating an immersion cooler together with a thermostatically controlled 300 W immersion heater. By maintaining the environment in which the tissue is placed at such a temperature, thermal gradients in the heated tissue are minimized.

A block diagram of the system is shown in Fig. 1. A coaxial cable connects the microwave generator (Microton 200, Electro-Medical Supplies, Wantage, Berks, 2450 MHz, 200 W CW, or MCL type 15155 MCL Inc. La Grange, Ill, USA, 400–1000 MHz 65 W CW) to a four-way power divider (type D4-2FN, Microlab/FXR, Livingston, NJ, USA) and each output of this device supplies power to one of four identical channels. Microwave power is fed into the input of a single-pole/four-throw coaxial switch (type A-14100, Transco Products Inc., Venice, Ca, USA). Two of the four outputs of the switch are connected by coaxial cable to waveguide applicators whilst a third output is connected to a coaxial termination (type 376NF, Narda Microwave Corp., Plainview, NY, USA). The fourth output on each switch is redundant in the present application. The output which is energized at any particular moment is determined by a control unit.

Microwave applicators

A pair of waveguide applicators is used in each of the four channels. The impedance mismatch between the applicators and the liquid bolus is reduced by means of quarter-wavelength transformers. Because the penetration depth for microwaves in tissue-like materials with high water content is small at the frequencies of interest (the microwave power is attenuated by a factor $1/e^2$ within about 17 mm at 2450 MHz and 30 mm at 915 MHz) the uniformity of heating in the experimental regions is improved by using pairs of applicators in parallel-opposed geometry. In order to avoid standing-wave effects the applicators are energized alternately by means of the control unit. Stray electro-magnetic fields are reduced by surrounding the ends of the waveguides and transformers by microwave-absorbing material.

The applicators are sections of standard WG10 (72 mm × 34 mm) rectangular waveguide excited in the TE_{10} mode by a coaxial-line probe antenna. This is a small coaxial line, terminated in the centre of the broad face of the guide, with its inner conductor extending a distance d into the guide. The probe is situated at a distance l from a short-circuiting plate across one end of the guide. For a probe of known diameter, the parameters d and l can be chosen so that almost all of the power incident along the coaxial line can be coupled into the waveguide (Collin, 1960). At 2450 MHz the applicators (supplied by Electro-Medical Supplies, Wantage, Berks.) are air-filled and are provided with tuning screws through the broad face of the guide for impedance matching. At 915 MHz the applicators are filled with a low loss dielectric material (Eccoflo HiK powder, Emerson & Cuming Inc., Canton, Ma, USA) with relative dielectric constant of 12.

Thermometry

Tissue temperatures are measured with PTFE covered copper/constantan thermocouples, approximately 200 μm in diameter, held perpendicular to

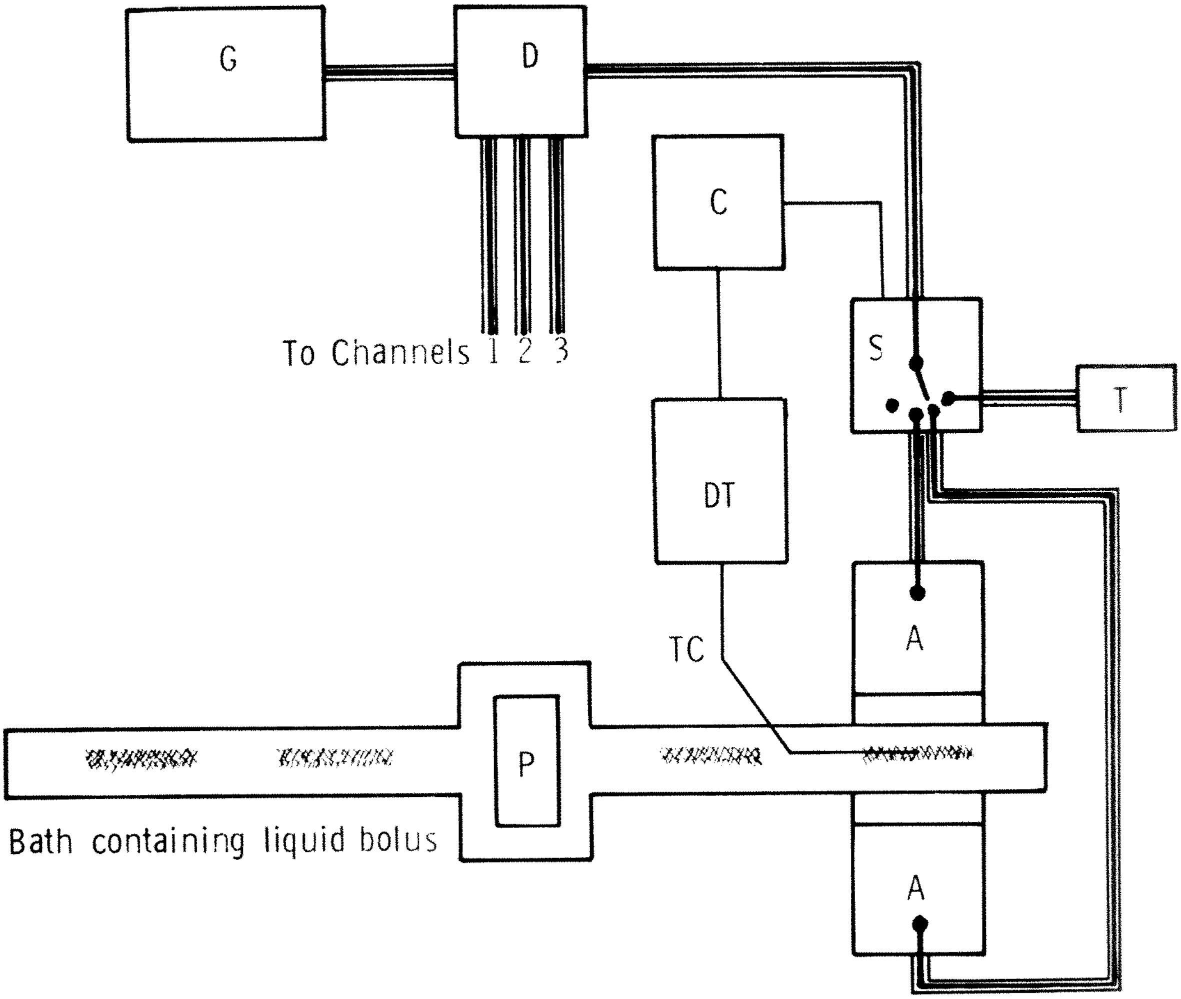

FIG. 1.

The heating system: only one of the four channels is shown. The hatched areas show the locations in the bath at which experimental animals are placed.

G microwave generator; D 4-way power divider; S coaxial switch; A waveguide applicator; T coaxial termination; TC thermocouple; DT digital thermometer; C control unit; P pumps, cooling device and thermostatically controlled heater.

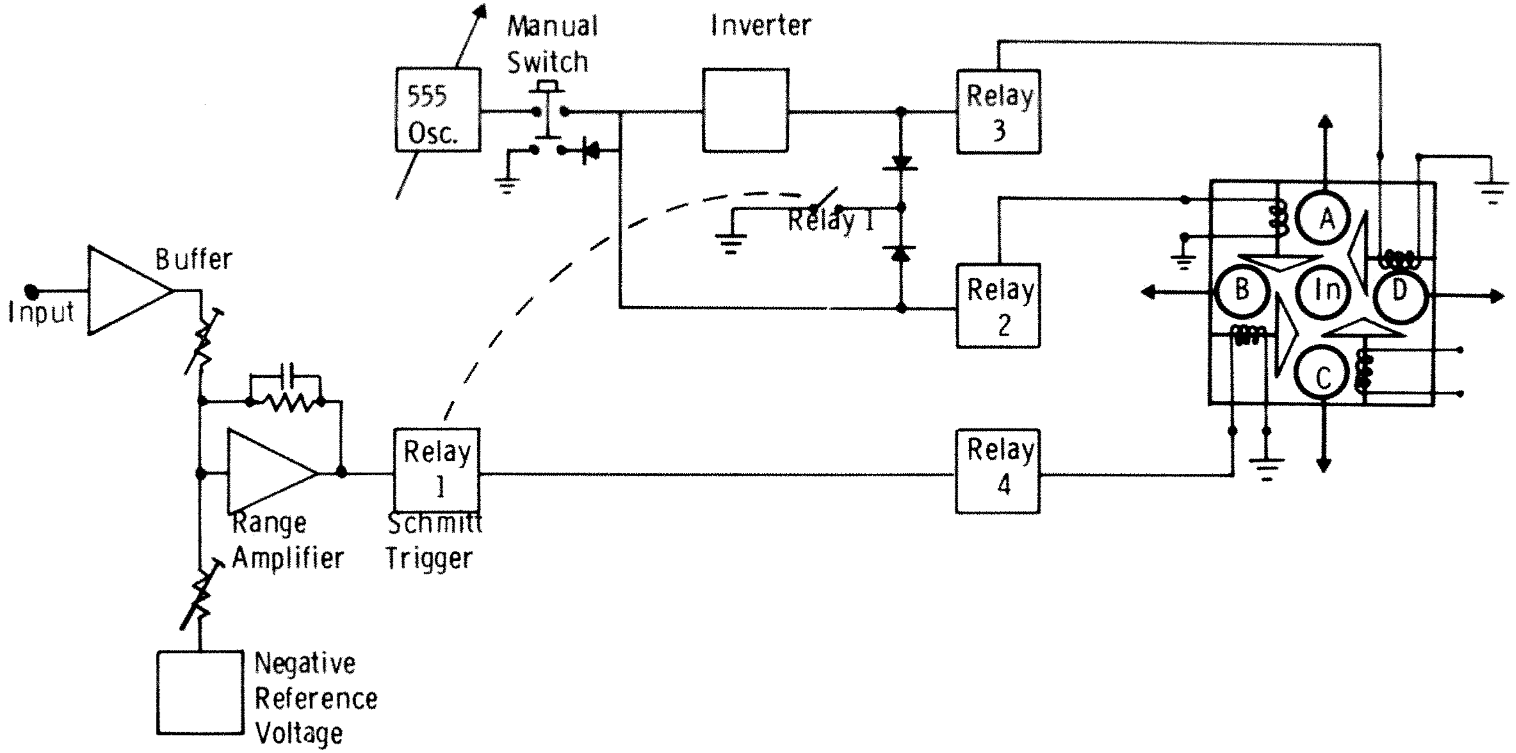

Fig. 2.
Schematic diagram of control unit and microwave switch. Coaxial outputs A and B of the microwave switch are connected to the waveguide applicators, whilst coaxial output C is connected to the matched termination. Output D is redundant.

the direction of the microwave electric field by means of supports made from small-bore Perspex tubing. The thermocouples are taken to the inputs of digital thermometers (type 5235, Comark Ltd., Rustington). Each thermometer is periodically calibrated against a secondary laboratory standard.

Control unit

A block diagram of the unit used to drive each of the coaxial switches is shown in Fig. 2. Further information, including a complete circuit diagram, may be obtained from the author by request. The output of a variable frequency (0–2 Hz) oscillator (555 timer integrated circuit) is fed directly to the driving circuit of relay 2 and via an inverting circuit to the driving circuit of relay 3. These relays are connected to the coaxial switch so as to energize the two microwave applicators alternately. An analogue output voltage from the digital thermometer is taken to the input of the control unit. After passing through a buffering circuit (LM310D, National Semiconductors) the signal is suitably scaled and added to an adjustable reference voltage by the 741 operational amplifier. The output of this device is taken to a trigger circuit which can energize relay 1. When the temperature indicated by the digital thermometer exceeds the desired value, relay 1 is energized; this energizes relay 4 whilst switching off relays 2 and 3. Relay 4 is connected to the coaxial switch in such a way that microwave power is directed to the coaxial termination. When the temperature falls below the desired value, microwave power is once more switched between the two applicators.

A facility for manual switching is also included in the control unit.

SYSTEM EVALUATION

In order to evaluate the system, pilot experiments were carried out with three rodent tissues which have been used in previously reported investigations where heating was achieved by immersion in hot water—mouse leg and foot (Stewart and Denekamp, 1977), rat tail (Myers and Field, 1977; Morris *et al.*, 1977), and exteriorized mouse jejunum (Hume *et al.*, 1979b).

Similar rates of increase in temperature were observed when the leg and foot were orthogonal with or parallel to the direction of the microwave electric field. The temperature in the leg, as monitored by thermocouples, could be maintained to within ±0.15°C at a temperature above that of the liquid bolus. When rodent tails are irradiated with microwaves in air, rapid heating occurs if the tail is parallel to the microwave electric field and only a small amount of absorption results when it is orthogonal to the field. When tails were immersed in the bolus and subjected to microwaves, heating showed little dependence upon orientation, and the tissue temperature could be maintained to within ±0.15°C at a temperature slightly in excess of that of the bolus.

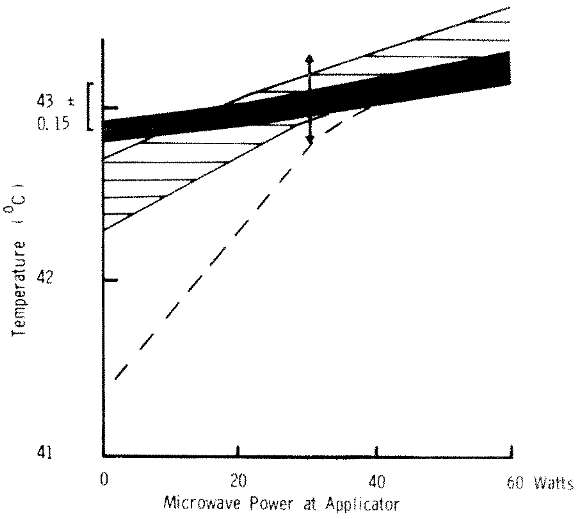

FIG. 3.

Temperatures monitored in the exteriorized mouse intestine subjected to 2450 MHz microwaves whilst immersed in liquid bolus maintained at 43±0.15°C. The dark and hatched areas represent 50% of measurements central to the median made "near to" and "far from" mesenteric blood vessels (see text). The broken line indicates the lowest temperatures observed at various microwave power levels. The power absorbed by the intestine was estimated to be approximately 100 times smaller than the powers shown on the abscissa. The arrow represents the full range of temperature observed at 30 W microwave power.

Figure 3 shows the temperatures monitored during microwave heating (2450 MHz) of the exteriorized mouse intestine. This biological system has previously been used to demonstrate the influence of blood flow on temperature distributions within tissues; full details of animal preparation have been reported elsewhere (Hume *et al.*, 1979b; Hand *et al.*, 1979b). Temperature measurements were achieved by inserting fine thermocouples through the jejunal wall either "near to" the mesenteric blood vessels of the exposed section of intestine or diametrically opposite ("far from") this region. The dark and hatched areas in Fig. 3 represent 50% of measurements central to the median of each group. In the absence of microwaves, temperatures "far from" the mesentery were typically 0.1–0.2°C below bolus temperature whereas those "near to" the mesentery were usually 0.3–0.7°C below bolus temperature. The results show that, by choosing an appropriate level of microwave power (about 30 W as measured at the applicator, in this case), the variation in temperature within the jejunal wall may be minimized.

Conclusions

A four-channel microwave heating system, designed for the treatment of small animals, has been described. The temperature of each region treated may be maintained to within approximately ±0.15°C and thermal gradients in the tissues may be minimized by adjustment of microwave power and liquid-bolus temperature.

It has been demonstrated that orientation of the tissue with respect to the microwave electric field does not affect significantly the absorption of microwaves by the tissue. The cooling effect of blood flow within tissue during microwave heating may be reduced from that observed when heating is by immersion in hot water.

Although this system is designed for the treatment of experimental animals, the technique of controlled switching of microwave power to a number of applicators should also prove to be of use in the treatment of patients. The heating of deeply lying tissues relative to superficial ones could be increased by using a number of direct contact applicators. The heating patterns produced in tissues by such applicators can be calculated (Ho, 1979) and, by proper choice of their relative positions and the duration and sequence in which they are energized, an optimum hyperthermia treatment can be envisaged. It is well known that many artefacts may appear in the measurement of temperature with thermocouples or thermistors in the presence of electromagnetic fields. The control of microwave power, either by modulation of the microwave generator or by switching into a dummy load, would allow reliable temperature measurements in the tissue to be made in the absence of microwaves.

Acknowledgments

I would like to thank Mr. F. C. A. Cobbett for construction of electronic equipment, Dr. S. P. Hume and Miss J. C. L. Marigold for assistance in the assessment of the heating system, Dr. S. B. Field and Prof. J. E. Robinson for helpful discussions, and other colleagues at the Cyclotron Unit for interest in this work.

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Book review

Radiation Protection in the Radiologic and Health Sciences. By Marilyn E. Noz and G. Q. Maguire Jr., pp. xii + 218, 1979 (Henry Kimpton, London), £8·75.
ISBN 0–8121–0657–1

The aim of this book is excellent—to provide a text for training radiographers, medical physicists and junior radiologists. The result is, however, not to be commended. It is full of half-truths ("the damage produced by ionizing radiation is cumulative") and blinding glimpses of the obvious ("For a unit density material, $\rho = 1$"). The sections on instrumentation read like the catalogue of certain well-known manufacturers. Several scales on graphs and nomograms betray evidence of amateur draughtsmanship. Any attempt to use this book for training would have to be accompanied by detailed explanation of what was meant.

Clearly, the authors know their subject, and there is evidence that they are better teachers than writers. Before there is any danger of this book being reprinted, they should enlist the help of a competent writer to examine critically every sentence, and re-write as necessary to convey the correct meaning without ambiguity. The result could then be of great value.

This review volume will be presented to the B.I.R. library as the reviewer will have no use for it.

S. B. Osborn.

1979, *British Journal of Radiology*, *52*, 989–990 DECEMBER 1979

Case reports

The ultrasonic diagnosis of bilateral hydronephrosis in twins during pregnancy

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(*Received June 1979*)

Much attention has been centred on the ultrasonic detection of fetal renal abnormalities *in utero* (Bartley *et al.*, 1977; Garrett *et al.*, 1970; Garrett *et al.*, 1975; Kaffe *et al.*, 1977a; 1977b; Keirse and Meerman, 1978; Lee and Blake, 1977; Santos-Ramos and Duenhoelter, 1975).

CASE HISTORY

A 22-year-old Pakistani lady, was referred to the Ultrasound Department of The London Hospital for abdominal ultrasound examination in September 1978, when she was about 23 weeks pregnant. At that time she was complaining of left-sided abdominal pain and had intermittent fever and vomiting.

Ultrasound examination of the maternal liver, pancreas, gall-bladder and kidneys showed no abnormality. Scanning of the uterus revealed a twin pregnancy, both fetuses lying transversely.

Both fetal abdomens appeared grossly abnormal, with bilateral transonic spaces at the sites of the kidneys, with no evidence of normal renal tissue. This was interpreted as representing bilateral hydronephrosis in both twins. There was liquor around both twins, indicating that urinary obstruction was not complete. Neither fetal bladder was identified at this examination, suggesting that there was no bladder outflow or urethral obstruction. BPD measurements of 5.7 cm were obtained. Fetal heart movement was seen in both fetuses.

Later in pregnancy, the patient moved to Oxford, where she was seen at approximately 38 weeks. An ultrasound scan then again showed the bilateral transonic masses in both twins. Urine was seen in the bladder of one twin but not the other.

A Caesarean section was performed. On exploration of the maternal abdomen, the maternal kidneys appeared normal. Both twins were apparently in good condition after birth, but X-ray and ultrasound examination of the babies confirmed the bilateral hydronephrosis in each case.

DISCUSSION

Recognition of fetal hydronephrosis during obstetric ultrasound scanning is important because increasing abdominal distension may impede vaginal delivery. The baby will require specialized paediatric management immediately after birth, and foreknowledge of this will save any unnecessary delay.

Hydronephrosis has been demonstrated *in utero* previously (Garrett *et al.*, 1975; Lee and Blake, 1977), but this would appear to be the first occasion on which bilateral hydronephrosis has been diagnosed *in utero* in twins.

Gee and Abdulla (1978) described the antenatal diagnosis of fetal duodenal atresia by ultrasonic

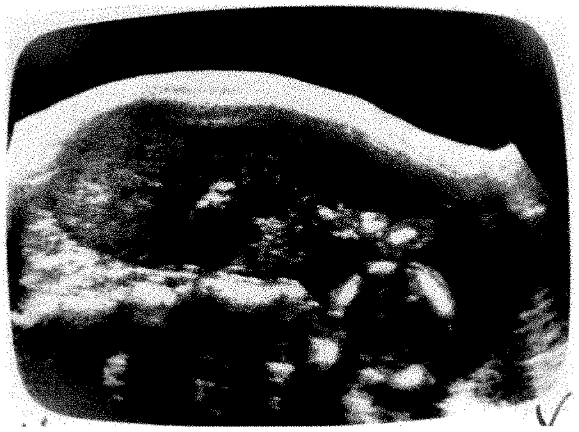

FIG. 1.

Sagittal scan of the maternal abdomen showing a transverse section through the trunk of twin 1. Large bilateral transonic masses are present.

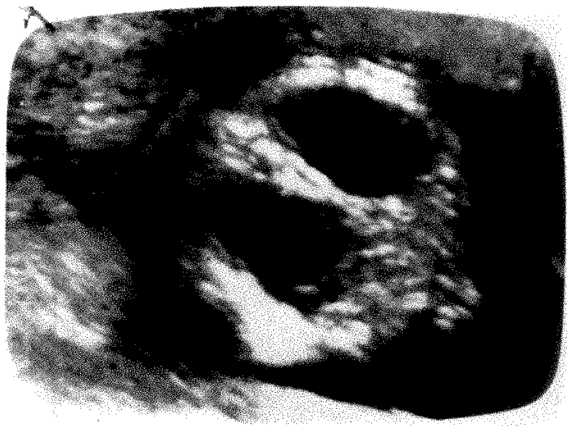

FIG. 2.

Transverse section of the fetal abdomen showing the bilateral hydronephrosis in greater detail.

1979, *British Journal of Radiology*, 52, 990–992

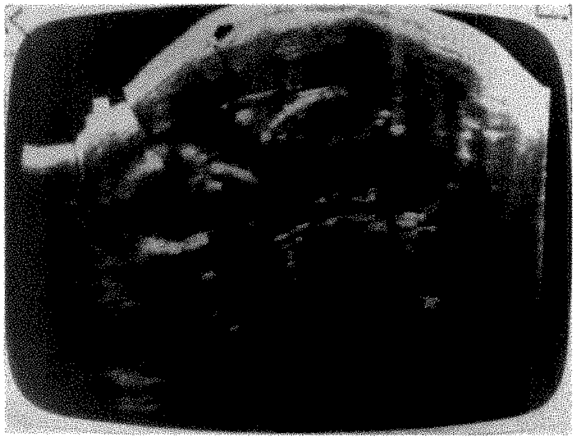

FIG. 3.

Transverse scan of the maternal abdomen showing similar transonic masses in twin 2.

scanning. A cross section of the upper fetal abdomen in their case showed double cystic structures corresponding to stomach and dilated proximal duodenum. This could represent a difficult differential diagnosis from bilateral hydronephrosis, and the possibility should be kept in mind, particularly if poly-hydramnios is present.

ACKNOWLEDGMENTS

We are grateful to Professor Huntingford and Professor Turnbull for permission to report the details of this patient who was under their care. We should also like to thank Dr. Metreweli for helpful advice.

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The features of the Mirizzi syndrome on ultrasound examination

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The Mirizzi syndrome consists of the following four elements:

1. an anatomic arrangement of the cystic duct such that it lies almost parallel to the common hepatic duct;
2. impaction of a gall-stone in the cystic duct or neck of the gall-bladder;
3. partial mechanical obstruction of the common hepatic duct by the stone itself or the resulting inflammatory reaction; and
4. recurrent cholangitis or ultimately cholangitic cirrhosis due to the partial obstruction (Clemett and Lowman, 1965).

This is an uncommon syndrome. We report the features on ultrasound examination in a patient we have recently seen.

CASE REPORT

A 71-year-old female was admitted to hospital following an episode of right upper quadrant pain, chills, fever and

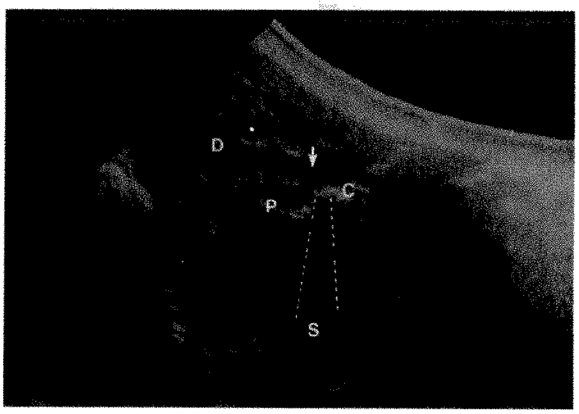

FIG. 1.

A longitudinal scan in the mid-line showing the dilated common duct (D) lying above the portal vein (P). The duct appears to stop (↓) just above an echo density (C) with distal acoustic shadowing (S).

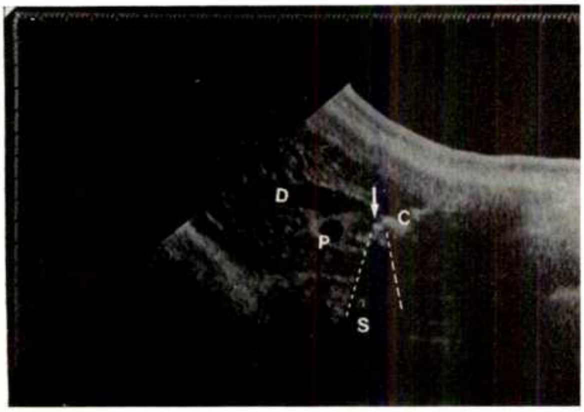

FIG. 2.

A similar section showing the common duct (D) narrowing (↓) down towards the calculus (C).
S—Acoustic shadowing. P—Portal vein.

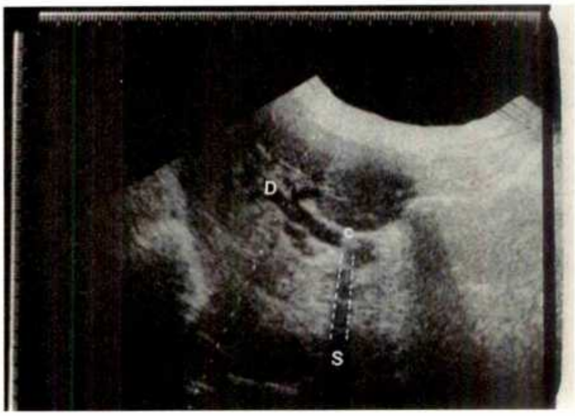

FIG. 4.

Longitudinal scan showing a calculus (C) within a dilated common duct (D).
S—Acoustic shadowing.

jaundice. Ten years previously gall-stones had been shown by an oral cholecystogram. The patient had refused cholecystectomy at that time. During the ten years she had remained fairly well, apart from infrequent episodes of right upper quadrant pain. As is the common practice in our hospital with jaundiced patients, she had an ultrasound examination within 48 hours of admission (Dewbury *et al.*, 1979). This showed the presence of dilated intrahepatic bile ducts and a dilated upper common duct measuring 13mm in diameter (Fig. 1). This large duct appeared to stop just below the porta hepatis and 1 cm below this point an echo density with marked distal acoustic shadowing was seen. This appearance is typical of a calculus. At the time of examination it was assumed that this calculus was in the common duct. In retrospect it clearly is not in the duct, and in Fig. 2 the common duct can be seen narrowing as it approaches the calculus. The patient's jaundice deepened and before proceeding to laparotomy a fine needle percutaneous transhepatic cholangiogram was done. This shows the typical features of the Mirizzi syndrome (Fig. 3). A large, faintly calcified calculus can be seen adjacent to the common hepatic duct and causing a broad curved impression on its lateral aspect. The duct is considerably narrowed at this point, causing partial proximal obstruction with dilation of the intrahepatic ducts. At laparotomy the chronically inflamed gall-bladder and a large calculus were removed.

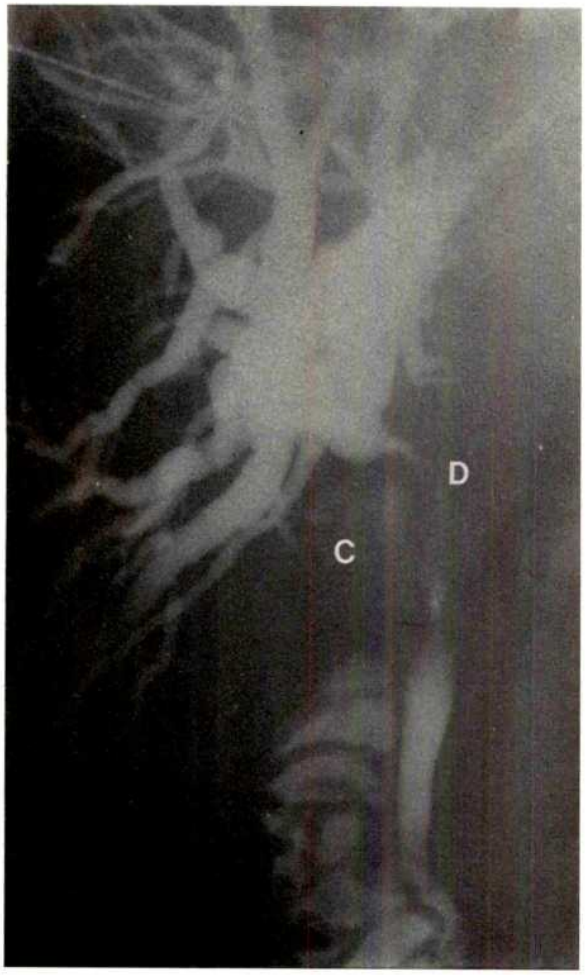

FIG. 3.

Fine needle percutaneous cholangiogram. This shows a dilated upper duct system with narrowing of the common hepatic duct (D) at the level of a faintly opacified calculus (C). The calculus and surrounding inflammatory reaction causes a typical broad curved impression on the lateral aspect of the duct.

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COMMENT

To make the diagnosis of a calculus in the common bile duct at an ultrasound examination it is necessary to show the calculus within the duct, which is often possible (Fig. 4). The Mirizzi syndrome is uncommon and the author was not fully aware of its features. With this knowledge, and applying strict ultrasound criteria, it should be possible to make a positive diagnosis. In retrospect, the ultrasound features are characteristic.

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Lipomatous tumour of the uterus: radiographic and ultrasonic appearance

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(Received March 1979)

Masses in the pelvis that are shown to contain fat on X-ray are usually thought to be ovarian in origin. An unusual lipomatous tumour of the uterus, seen on plain radiographs and on ultrasound, is presented. This is the first report of the pre-operative demonstration of such a tumour by X-ray or ultrasound.

CASE REPORT

A 59-year-old white female was admitted for evaluation of a pelvic mass. She had been in good health until four days prior to admission when she noted pain in her right hip and a sensation of pressure in her pelvis. Physical examination revealed a large, hard, irregular pelvic mass extending upward to the level of the umbilicus. On the plain film of the abdomen there was a rounded mass in the pelvis measuring approximately 18 cm in diameter. The central portion of this was radiolucent and surrounded by a relatively uniform soft tissue density measuring 1–2 cm in thickness (Fig. 1). Abdominal ultrasound demonstrated a 16 cm mass with a strongly echogenic central portion, which was surrounded by a relatively echo-free border (Fig. 2). The central portion of the mass was so attenuating that the back wall could not be seen. The radiographic and ultrasonic findings were interpreted as a soft-tissue pelvic mass with a fatty central core and assumed to represent a dermoid tumour of the ovary. At operation, the mass was found to be within the uterus and was thought to be a fibroid tumour. Total hysterectomy was performed. Gross examination of the uterus showed a large, spherical, firm mass, which on cut section was seen to be within the myometrium.

It was well circumscribed and yellowish in colour. Microscopically, the tumour was composed predominantly of mature fat cells with some interposed fibrous elements and smooth muscle. The pathologic diagnosis was fibromyolipoma of the uterus.

DISCUSSION

Lipomatous tumours of the uterus are relatively uncommon. Salm (1973) found seven cases 5200 speciments over a 25 year period, an incidence of 0.14%. Brandfass and Everts-Suarez (1955) summarized the world literature in a comprehensive review. They found 33 pure lipomas and 63 mixed tumours (fibromyolipomas, myolipomas and fibrolipomas) with varying amounts of fibrous and smooth muscle tissue. Most patients are postmenopausal, predominantly in their 50's and 60's although one was 23 years old. The size of the tumours vary from several millimetres to 32 cm in diameter. They may occur anywhere within the uterus, but are however, predominantly found in the corpus. Most are associated with ordinary fibroids. Grossly, they are rounded or oval and well encapsulated. The pure lipomas are soft and yellow, while the more fibrous tumours tend to be lighter in colour and firmer. Clinically, the symptoms are indistinguishable from those of ordinary fibroids. Histologically, the pure lipomas consist of mature fat cells in a spare connective tissue stroma. The

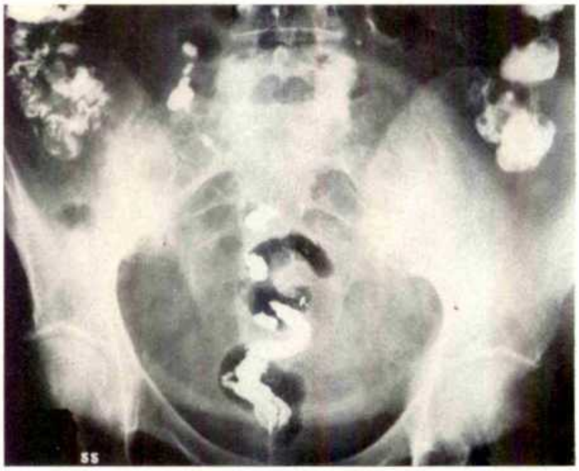

FIG. 1.

Radiolucent central mass corresponds to fatty tumour. A thin rim of more radiodense material, representing the myometrium, surrounds it.

1979, *British Journal of Radiology*, *52*, 993–995

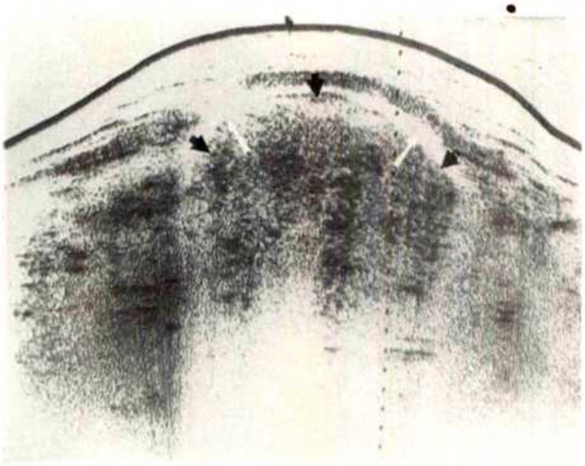

FIG. 2.

Transverse supine B-scan 6 cm above the symphysis. The strongly echogenic mass (black arrows) corresponds to the fatty tumour. Note how sound is absorbed, producing a shadow and obscuring the back wall. The narrow, relatively sonolucent rim (white arrows) corresponds to the myometrium around the tumour.

mixed type of fatty tumour has varying degrees of fibrous stroma and muscle tissue. The histogenesis of these tumours is uncertain. The two most popular theories are that they arise from: (1) misplaced embryonic fat cells in the uterus, or (2) fatty metaplasia of muscle or connective tissue cells.

The recognition of fatty tumours by virtue of their relative radiolucence on standard radiographs is well known. Behan and Kazam (1978) have described the ultrasonic characteristics of fatty tissues and tumours in multiple locations throughout the body. They found that in the majority of instances fat is strongly echogenic and may cast an acoustic shadow preventing the demonstration of the entire mass, as in this case. Only rarely do fatty tumours appear echo-free. While in most instances a tumour of the pelvis which is seen to be composed of fatty tissue by either X-ray or ultrasound will be of ovarian origin, a lipomatous tumour of the uterus should be considered. This is the first reported case of a fatty tumour of the uterus being demonstrated on X-ray and ultrasound.

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Neuroblastoma in a child with the hydantoin and fetal alcohol syndrome. The radiographic features

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(*Received April 1979 and in revised form June 1979*)

Fetal alcohol and fetal dilantin (hydantoin) syndromes have been recognized only recently. Both have distinguishing features mainly characterized by peculiar facies, cardiovascular disorders, psychomotor retardation, limbs and skeletal anomalies (Jones *et al.*, 1973; Hanson *et al.*, 1976; Meadows, 1968; Hill *et al.*, 1974; Goodman *et al.*, 1976; Dabee *et al.*, 1975). The association of malignant tumours in children with fetal alcohol or fetal dilantin syndrome has been documented, although rarely (Hornstein *et al.*, 1977; Blattner *et al.*, 1977). Only two previous cases of neuroblastoma associated with fetal hydantoin syndrome have been reported (Pendergrass and Hanson, 1976; Sherman and Poizen, 1976). We are reporting a third case born to a mother who was alcoholic and taking diphenylhydantoin for a seizure disorder.

CASE REPORT

A 35-month-old child was admitted to Cook County Children's Hospital for investigation of his cardiac murmur and failure to thrive. His mother was an alcoholic and had been taking diphenylhydantoin sodium (Dilantin) for seizure disorder. On an intravenous urogram following cardioangiography, the left kidney was noted to be displaced downwards (Fig. 1). A left supra-renal mass was strongly considered and further investigation initiated.

The relevant examination included a hyperactive child with gross motor and mental retardation. He had a peculiar facies with hypertelorism, bilateral ptosis, increased epicanthal folds, high arched palate and frontal bossing. A loud systolic murmur was heard along the left sternal border. There was a left abdominal mass on deep palpation. The tips of the toes were hypoplastic, especially the 5th, bilaterally. This was confirmed on radiographs (Fig. 2). Fetal dilantin syndrome with associated neuroblastoma and ventricular septal defect was diagnosed. A chest film showed an elevated right hemidiaphragm due to an eventration (Fig. 3).

The urine vanilyl mandelic acid level was normal; the ultrasonogram outlined a solid mass. A skeletal survey

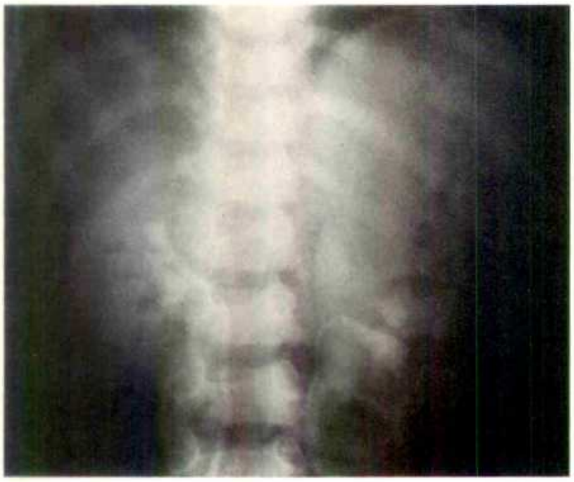

FIG. 1.

Frontal view of excretory urogram shows left kidney displaced downwards and laterally. There is duplication of the collecting systems.

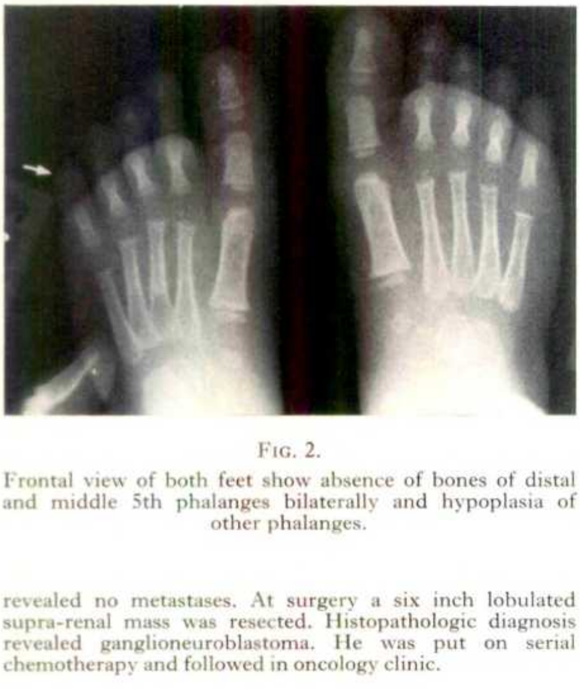

FIG. 2.

Frontal view of both feet show absence of bones of distal and middle 5th phalanges bilaterally and hypoplasia of other phalanges.

revealed no metastases. At surgery a six inch lobulated supra-renal mass was resected. Histopathologic diagnosis revealed ganglioneuroblastoma. He was put on serial chemotherapy and followed in oncology clinic.

DISCUSSION

This child presented with features of both the fetal alcohol and the fetal dilantin syndromes, albeit with more hallmarks of the latter.

Jones *et al.* (1973) and Hanson *et al.* (1976) have described children with clinical manifestations of fetal alcohol syndrome which consisted of developmental delay, microcephaly, pre- and postnatal growth deficiency, short palpebral fissures, maxillary hypoplasia, widened epicanthal folds, joint anomalies, cardiac defects and altered palmar crease. Meadows first described fetal hydantoin syndrome in 1968 followed by several other reports (Hill *et al.*, 1974; Goodman *et al.*, 1976; Dabee *et al.*, 1975). These children have features consisting of cleft lip and palate, congenital heart defects (most commonly ventricular septal defect), skeletal anomalies (predominantly hypoplastic digits and nails), central nervous system malformations, especially microcephaly and hydrocephalus, and varying degrees of mental and motor retardation. Their facies includes frontal bossing, asymmetry, hypertelorism, broad nasal bridge, thin lips and long philtrum (Meadows, 1968; Hill *et al.*, 1974; Goodman *et al.*, 1976; Dabee *et al.*, 1975). Findings may be similar in both syndromes.

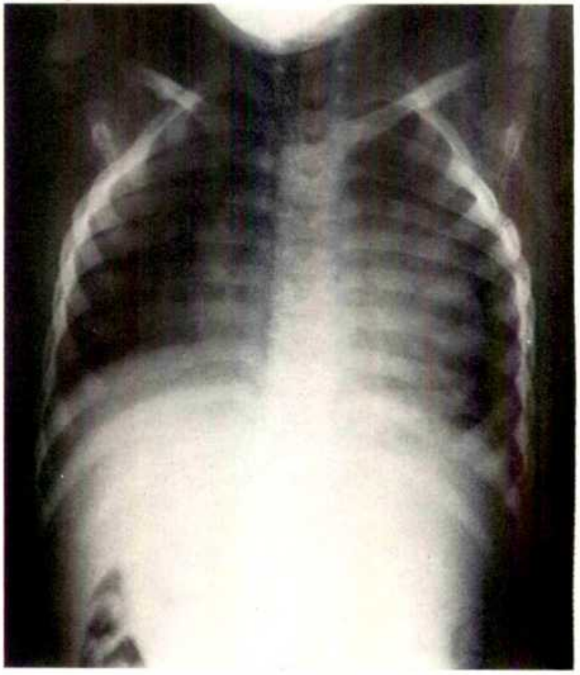

FIG. 3.

Frontal view of the chest shows cardiomegaly and eventration of the right hemidiaphragm. Ribs are somewhat thickened and relatively horizontal in position.

Very uncommon is the association of fetal dilantin syndrome with neuroblastoma. There have been only two cases of neuroblastoma so reported, one in a three-year-old child and the other a seven-day-old baby (Pendergrass and Hanson, 1976; Sherman and Poizen, 1976). Both mothers had seizure disorders and were on phenytoin for several years. The only other malignancy reported in this group is a malignant mesenchymoma of the liver in a patient with associated phenytoin cleft lip and palate (Blattner *et al.*, 1977).

Diphenylhydantoin has been shown to cross the placenta with the highest concentration in the liver, heart and adrenal glands. The pathogenesis of its teratogenesis and carcinogenesis remain obscure, although it is presumed that there is formation of epoxides as intermediary metabolites which are carcinogenic, mutagenic, cytotoxic and teratogenic. Changes in the folic acid metabolism in chronic hydantoin ingestion may also be a contributory factor (Mirkin, 1971).

ADDENDA

The clinical aspects of this patient were reported in detail by Seeler *et al.*, 1979.

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Posterior intrathoracic goitre as a cause of thyrotoxicosis

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Most patients with thyrotoxicosis have a palpable goitre although the degree of thyroid enlargement varies considerably. In 1–3% of cases, however, the hyperfunctioning thyroid gland is not significantly enlarged on clinical examination or on scintiscan (Werner, 1978). We report an unusual case of thyrotoxicosis in a patient who had no palpable goitre in the neck but was found to have a solitary intrathoracic toxic thyroid nodule behind the trachea.

CASE REPORT

A 60-year-old woman was admitted to hospital in May 1978 with a two week history of increasing dyspnoea, ankle swelling and recurrent haemoptyses without chest pain. She had complained of a productive cough for many years associated with cigarette smoking. In 1974, she was found to have mild diabetes mellitus which was managed with a diet and chlorpropamide. Her serum thyroxine measured at that time to exclude hypothyroidism as a cause of her obesity was normal.

On examination she was slightly overweight and had signs of moderately severe congestive cardiac failure and atrial fibrillation confirmed on ECG and blood pressure of 150/100. She had no cardiac murmur, fever or finger clubbing. Her hands were warm and moist and she had a slight tremor. There was no palpable goitre and her eyes appeared normal.

Chest X-ray (Figs. 1 and 2) showed on the lateral film a 5 cm diameter mass above the aortic arch extending from the posterior wall of the trachea to the dorsal spine. The trachea was slightly bowed anteriorly and there was evidence of old tuberculous disease with calcification in the right upper lobe. A ventilation/perfusion lung scan showed no evidence of pulmonary embolism to account for her haemoptyses. Thyroid function tests confirmed a clinical diagnosis of hyperthyroidism with serum total triiodothyronine of 5.0 nmols/l (normal range: 1.2–3.0) and serum thyroxine of 200 nmols/l (normal range: 70–190). A thyroid scan (Fig. 3) following intravenous injection of $^{99}\mathrm{Tc}^{\mathrm{m}}$ pertechnetate, using a gamma camera fitted with a pinhole collimator (Ng Tang Fui and Maisey, 1979a) showed an intrathoracic hyperfunctioning nodule corresponding to the retrotracheal mass on chest X-ray, with no uptake in the neck.

A diagnosis of thyrotoxicosis due to an autonomously functioning intrathoracic thyroid nodule was made, complicated by atrial fibrillation and cardiac failure. The haemoptyses were thought to be secondary to heart failure. She was treated initially with carbimazole, frusemide and digoxin with considerable improvement of her condition. In view of her chronic lung disease and cardiac complications, she was considered a poor risk for surgical excision of the intrathoracic goitre and was treated with 555 MBq (15 mCi) of ^{131}I under close supervision.

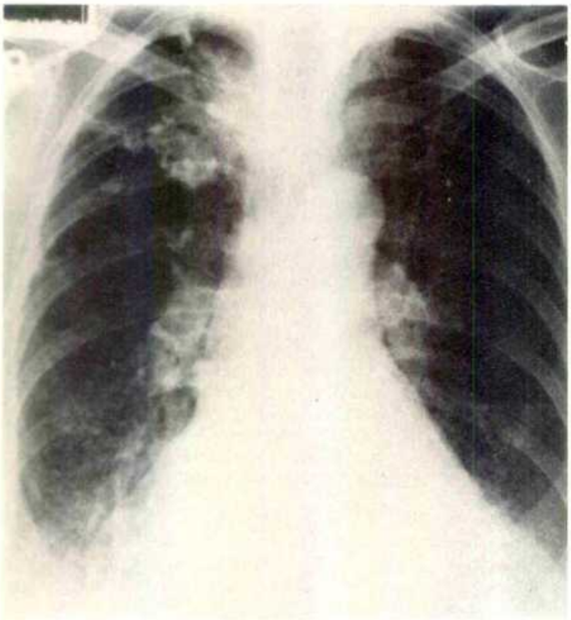

FIG. 1.
Chest X-ray film (PA) on admission.

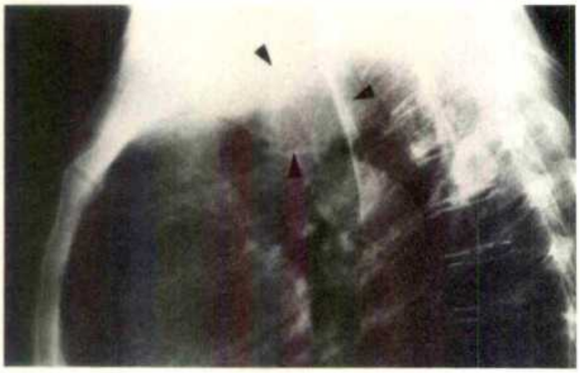

FIG. 2.
Left lateral chest X-ray film on admission showing a superior mediastinal mass (arrowed) behind the trachea.

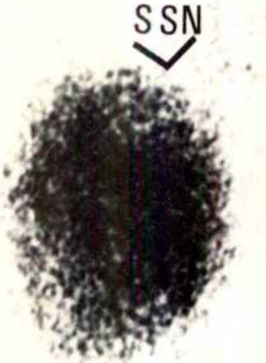

FIG. 3.
$^{99}Tc^{m}$ thyroid scan showing a solitary hyperfunctioning thyroid nodule below the level of the suprasternal notch (SSN) without any uptake in the cervical thyroid.

Within six months of the radioiodine therapy and without carbimazole for three months, she was clinically euthyroid although atrial fibrillation persisted. Her serum triiodothyronine and thyroxine concentrations were normal at 1.8 and 81 nmols/l respectively. A repeat thyroid scan (Fig. 4) showed resolution of the toxic nodule with some uptake in the previously suppressed cervical thyroid.

DISCUSSION

Retrosternal goitre usually represents extension of an enlarged cervical thyroid into the superior mediastinum. Less commonly, the thyroid gland is not palpable in the neck (Sherman and Shahbahram, 1966) and further investigations are required to establish a diagnosis of retrosternal goitre as the cause of an upper mediastinal mass on chest X-ray. Radioisotope scanning using ^{131}I is diagnostic if thyroidal uptake is demonstrated below the level of the sternal notch, but often uptake in retrosternal goitres is poor or absent and the diagnosis cannot be made or excluded by this technique (Hoffer *et al.*, 1976). Intrathoracic goitres are usually situated anteriorly in the superior mediastinum, but in one series 25% were situated posteriorly (Rietz and Werner, 1960).

Patients with intrathoracic goitres are usually euthyroid and may be asymptomatic or may have signs or symptoms related to compression of the trachea, oesophagus or superior vena cava (Rietz and Werner, 1960; Lesavoy *et al.*, 1975). Although slight retrosternal extension of a large cervical goitre is frequently encountered in patients with thyrotoxicosis, a toxic goitre that is essentially or entirely intrathoracic is rare (Rietz and Werner, 1960; Reeve *et al.*, 1962), and may cause diagnostic and therapeutic problems.

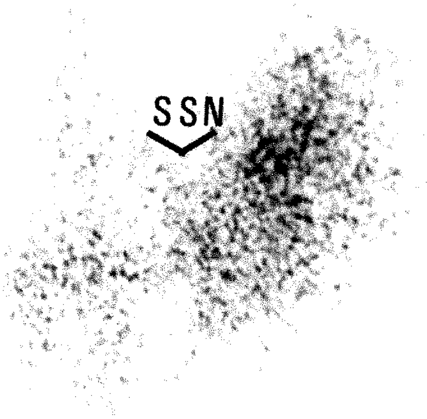

Fig. 4.

^{99}Tc^{m} thyroid scan six months after ^{131}I therapy, showing resolution of the hyperfunctioning nodule and uptake in the previously suppressed cervical thyroid.

Our patient presented with the typical cardiac manifestations of late onset thyrotoxicosis, *i.e.* atrial fibrillation and cardiac failure, but she had no palpable goitre. The mediastinal mass seen on chest X-ray was shown on scanning to be a toxic autonomous thyroid nodule suppressing the rest of the thyroid which is characteristic of uninodular Plummer's disease (Ng Tang Fui and Maisey, 1979b). Although ^{99}Tc^{m} pertechnetate is preferred to ^{131}I in routine thyroid scanning owing to its short half-life, lower gamma energy emission without any beta particles, and short study time, it is generally considered less suitable for investigation of retrosternal goitres in view of the high absorption of the 140 keV γ rays by the chest wall and the high blood background. In this patient, however, the ^{99}Tc^{m} scan successfully demonstrated the intrathoracic thyroid nodule owing to its relatively high uptake.

While intrathoracic goitres with or without hyperthyroidism are generally considered an indication for surgical treatment (Reeve *et al.*, 1962), radioiodine therapy after the initial course of carbimazole was considered more appropriate in this patient in view of her poor operative risk and the fact that she had a single hyperfunctioning nodule which usually responds well to a single large dose of ^{131}I (Ng Tang Fui and Maisey, 1979b) and is less likely to cause complications compared with a diffuse goitre. There were no immediate complications of the radioiodine therapy and treatment was successful as confirmed by the repeat scan after six months and the return to normal of her thyroid function tests.

ACKNOWLEDGMENTS

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We thank Professor Keen for referring this patient for investigation and treatment.

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Case reports

Mucocoele of the sphenoid sinus complicating fibrous dysplasia

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(*Received October 1978 and in revised form June 1979*)

Mucocoeles of the sphenoid sinus are rare (Nefson, 1957). A case is presented where such a lesion occurred in an area affected by fibrous dysplasia, a previously unreported combination.

Case History

A 25-year-old woman was referred to the Wessex Neurological Centre having rapidly become blind in the left eye ten days earlier. The vision in her right eye then deteriorated progressively such that on admission she was completely blind. There was no history of earlier visual disturbance, chronic sinus disease or craniofacial trauma. Examination confirmed that she was totally blind and the pupils were fixed and dilated. There was slight left proptosis but no orbital or facial asymmetry.

Skull radiographs demonstrated density and obliteration of the left ethmoidal air cells especially the posterior group. There was bulging and partial bony destruction of the orbital plate of the left ethmoid extending to the nasal septum with obliteration of the left nasal airway. The basisphenoid was also destroyed across the full width of the floor of the pituitary fossa with involvement of the left optic canal and the medial half of the right optic canal. There was marked developmental asymmetry of the lesser wings of the sphenoid. Computerized tomographic (CT) scanning confirmed the plain radiographic findings. In particular, the left ethmoidal and orbital deformities, together with the destruction of the optic canals, were well shown in the transverse axial plane. The left eyeball was distorted by local pressure and the left optic nerve was deviated.

The sclerosis and more particularly the sphenoid and orbital deformities were taken to indicate longstanding abnormality. Fibrous dysplasia was regarded as a possibility. The destructive element was obviously more recent and associated with the rapid clinical change. It was thought possible that malignant change had taken place in the underlying lesion (Jaffe, 1958; Aegerter and Kirkpatrick, 1963; Greenfield, 1969).

In an attempt to relieve the pressure on the optic nerves, radiotherapy was immediately instituted. Subsequent biopsy of the posterior ethmoids showed fibrous dysplasia. A bifrontal craniotomy was performed and both optic nerves were found to be encircled by a mucocoele of the sphenoid sinus. Haemorrhage had occurred into the mucocoele and this was felt to be the reason for the sudden deterioration of her vision. The optic nerves were decompressed, but her visual function did not recover.

Discussion

Mucocoeles of the sphenoid sinus are uncommon, the series of Zizmor and Noyek (1968) suggesting that they constitute 1% of all mucocoeles. Nugent *et al.* (1970), reviewing the world literature, found a total of eighty-five case reports. In nineteen of these the clinical information was sparse and these together with three reports that were not translated were eliminated from their analysis which was confined to the remaining sixty-three patients. The outstanding clinical feature was headache, characteristically frontal or periorbital and unilateral. This was not so in the present patient, but her presentation with progressive bilateral second and third nerve palsies and external ophthalmoplegia is otherwise typical.

This is confirmed by other authors (Nefson, 1957; Hayes, 1964; Hakuba *et al.*, 1975) and they emphasize the difficulty of distinguishing from ophthalmoplegic migraine if there be spontaneous remission, or more commonly from an intracranial lesion, usually a pituitary tumour.

As with the more common mucocoeles of the other paranasal sinuses, (Jackson, 1977), there is frequently a history of allergic rhinitis, nasal polyps or chronic sinusitis. There was no such history in the present case. Mucocoeles are usually considered to be simple retention cysts of the sinuses resulting when the drainage is blocked. They may, however, occur when an ostium is open and blockage of an ostium does not always result in a mucocoele.

Fibrous dysplasia, causing sclerosis and expansion of the skull base, is seen fairly frequently (Leeds and Seaman, 1962). Samy *et al.* (1967) and Grabias and Campbell (1977) have suggested that an expanding bone lesion of this type could occlude the ostium of the sphenoid sinus. We cannot, however, find any reference to the associated development of a mucocoele and Nugent *et al.* (1970) do not mention this possibility in their review. Other foramina, *e.g.* the optic canals, not uncommonly show narrowing in association with the bone thickening of fibrous dysplasia (Leeds and Seaman, 1962). In the present case, the absence of any other cause of occlusion of the sphenoid sinus suggests that this might have occurred. This would be similar to the development of a mucocoele of the frontal sinus when the frontonasal duct is occluded by an osteoma (Jackson, 1977).

The radiological features of mucocoeles of the sphenoid sinus were described by Norman and Yanagisawa (1964) and Hakuba *et al.* (1975). The sinus is opaque with destruction of its interseptum and the floor of the pituitary fossa. This destruction may extend into the posterior clivus and dorsum sellae or forwards into the anterior clinoid processes. The optic foramen and superior orbital

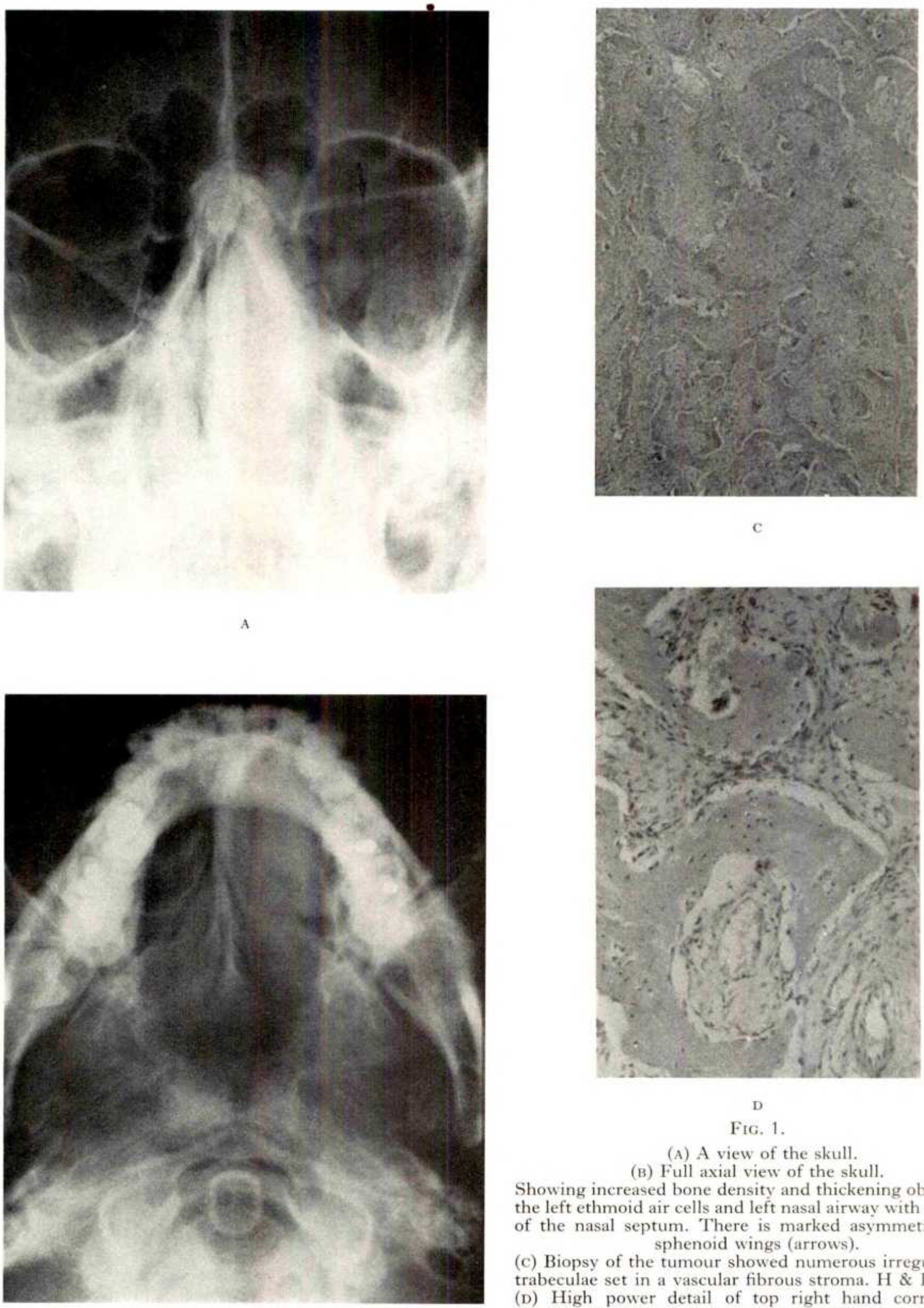

FIG. 1.

(A) A view of the skull.
(B) Full axial view of the skull.
Showing increased bone density and thickening obliterating the left ethmoid air cells and left nasal airway with deviation of the nasal septum. There is marked asymmetry of the sphenoid wings (arrows).
(C) Biopsy of the tumour showed numerous irregular bony trabeculae set in a vascular fibrous stroma. H & E × 125.
(D) High power detail of top right hand corner of A. showing the lack of appositional osteoblastic activity along the margins of the bone. H & E × 320.

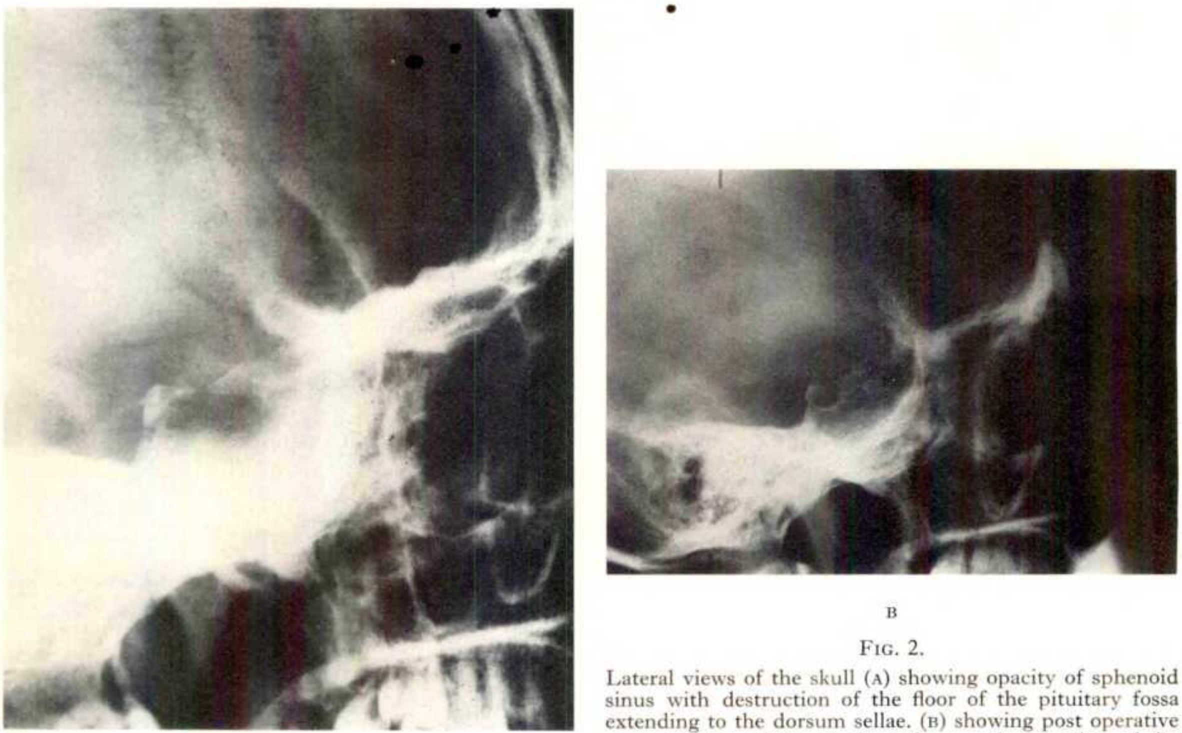

FIG. 2.

Lateral views of the skull (A) showing opacity of sphenoid sinus with destruction of the floor of the pituitary fossa extending to the dorsum sellae. (B) showing post operative reconstitution of the pituitary fossa and reaeration of the sphenoid sinus.

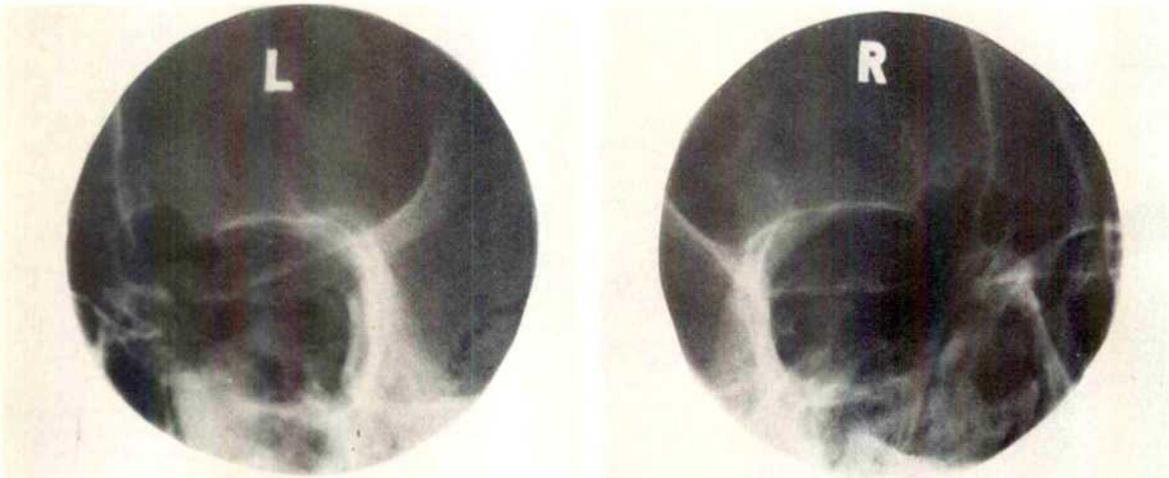

FIG. 3.

Views of the optic canals showing complete loss of definition of the left canal and loss of the medial margins of the right canal.

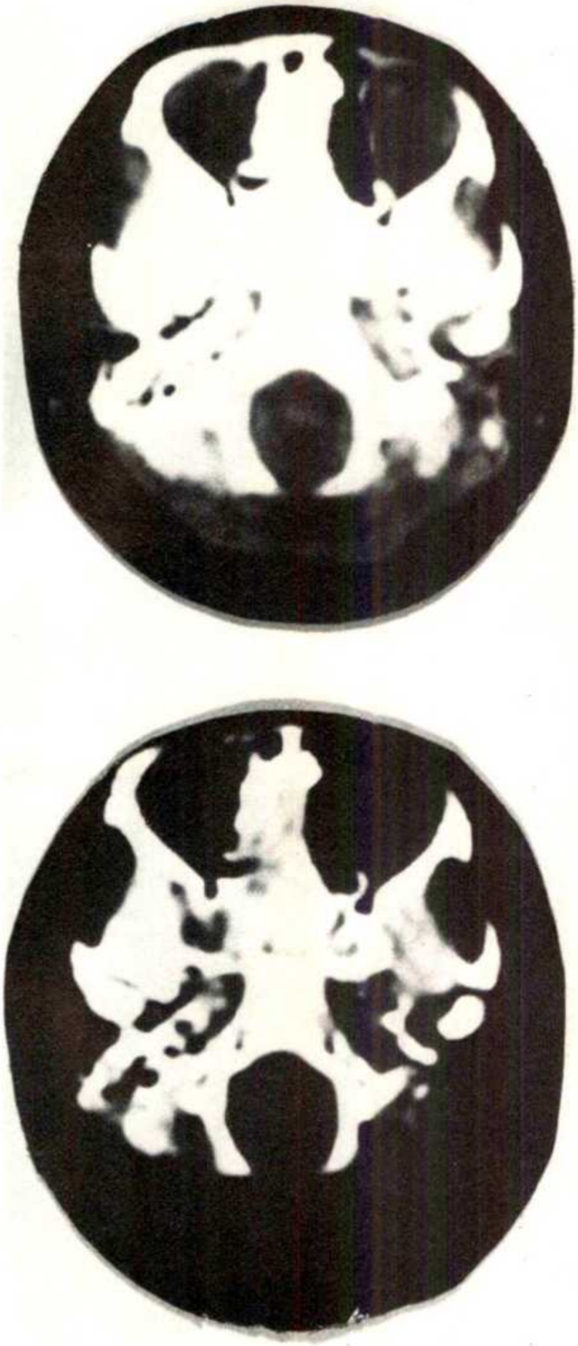

FIG. 4.

CT Scan views showing bony obliteration of the left ethmoid air cells and upper nasal airway with encroachment on the left orbit and displacement of orbital contents. The thickening extends posteriorly as far as the optic canal but the apex of the orbit is unaffected. The dorsum sellae is thinned and there is asymmetry of the sphenoids.

fissure may be widened and eventual extension into the ethmoid air cells may displace the lamina papyracea into the orbit.

In the present patient (Figs. 1–3), the sphenoid sinus was opaque and the floor of the pituitary fossa destroyed with loss of definition of both optic canals. In addition bone sclerosis and thickening due to fibrous dysplasia caused asymmetry of the sphenoid wing and obliterated the left ethmoids and left nasal airway, obscuring some of the features described above. CT scanning (Fig. 4) provided confirmation of the plain film findings and gave additional information about the extent of the lesion. The destruction of the sphenoid and the optic canals was demonstrated and the displacement of the orbital contents was shown to be due to bone thickening and not to direct invasion of either orbital apex. Nevertheless the exact nature of the destruction could not be diagnosed.

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Case reports

Peritoneal mesothelioma with unusual metastases

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Malignant peritoneal mesothelioma is rare. A case is reported with an unusual metastasis and an exceptionally long survival time. Radiographic, ultrasonic, scintigraphic and surgical findings are presented and the literature reviewed.

CASE HISTORY

A 34-year-old female with no history of asbestos exposure suffered four months fever, peri-umbilical cramps, vomiting, weight loss, and pain in the bladder area during micturition. Examination showed moderate abdominal distention. Investigations: chest radiograph normal; intravenous pyelogram: (Fig. 1) slight hydronephrosis above a compressed right ureter in the pars sacralis area. A barium follow through showed medial displacement of the small intestinal loops in the left iliac fossa (Fig. 2). Ultrasound (Fig. 3) revealed tumour masses covering the wall of the pelvis and surrounding the bladder. The patient had a laparotomy (June 1975) when massive tumour growth was found in the peritoneal and retroperitoneal spaces. There was thickening of the entire peritoneum which was covered with coarse greyish white nodules of varying size. Tumour tissue masses in the pelvis coated the pelvic wall and infiltrated the bladder. There was free ascitic fluid. The internal genital organs were normal. Both histology and cytology of the masses indicated peritoneal mesothelioma of adenomatous papillary form. Post-operatively, treatment with cytotoxic drugs and grid irradiation of the abdomen was performed. Apart from an episode of bilateral costophrenic sinus pleural effusions in 1975, the patient made a good recovery. In November 1977 a rectocele necessitated surgery. A vaginal hysterectomy with removal of adnexa was performed. The histological diagnosis of the massive tumour in the pouch of Douglas again confirmed mesothelioma.

There was no indication of a primary uterine or adnexal tumour, so excluding a metastasizing papillary serosal ovarian cell carcinoma. After further X-ray therapy and cytotoxics, the patient is now well and active despite the presence of small nodules throughout the lungs, presumably metastatic.

DISCUSSION

Until recently the malignant mesothelioma originating from the serosal peritoneum was a rare tumour of unknown etiology, Winslow and Taylor (1960) finding only 13 well documented cases. Elmes (1972) and Kannerstein and Churg (1977) have since reported a considerable increase in this disease, there

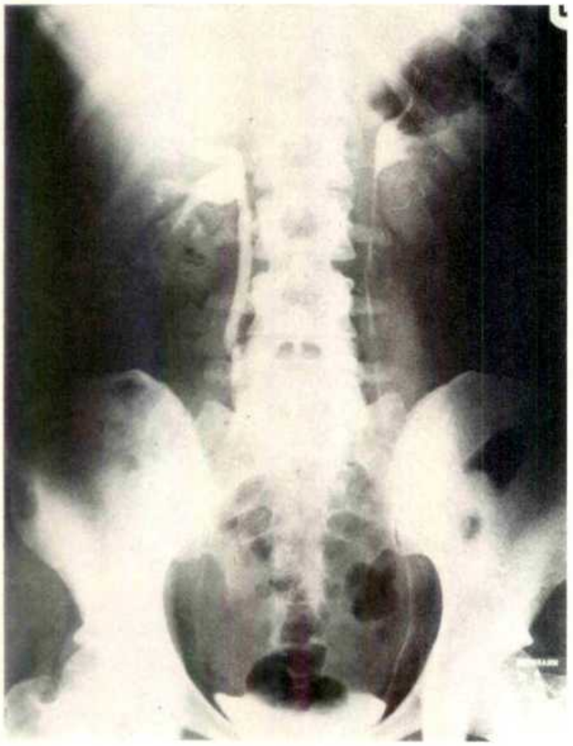

FIG. 1.

IVP: compression of the right ureter in the pre-sacral area.

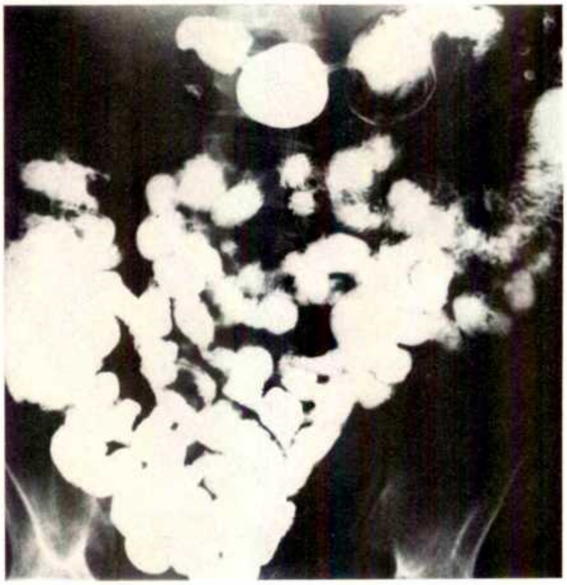

FIG. 2.

Barium follow through: barium filled ileum displaced medially from left iliac fossa.

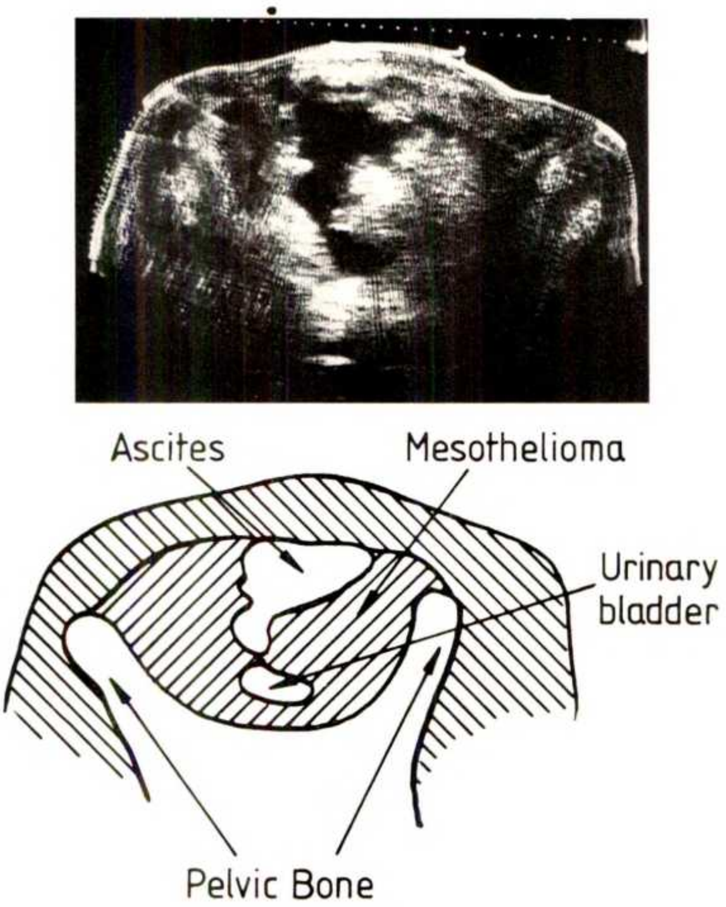

FIG. 3.

Ultrasound transverse section through pelvis: pelvic wall covered with tumour masses, tumour infiltration into the urinary bladder wall.

being 69 cases of it in the United States since 1964. This may be related to increased exposure to asbestos (Wagner *et al.*, 1960; Newhouse, 1972) and also to the greater attention given to research into those with known asbestos exposure (Moertel, 1972).

The characteristic clinical symptoms are abdominal pain and attacks of colic with vomiting. Tumour masses may be palpable. Ninety per cent of patients have ascites (Moertel, 1972). Anatomically there are two overlapping types of the disease: one, large localized tumour masses especially in the upper abdomen with infiltration of liver, pancreas and other gastrointestinal or retroperitoneal organs (Kannerstein and Churg, 1977). Additionally small nodules may be disseminated over both the visceral and parietal peritoneum. In the other form, diffuse partially confluent tumour plaques cover the entire peritoneal cavity wall up to 5 cm in thickness, leading to displacement, compressing the right ureter and bladder and causing rectal prolapse.

The diagnostic criteria established by Winslow and Taylor (1960) are compatible clinical history and physical signs, characteristic histology and progressive growth of the tumour resulting in death of the patient, generally in less than 12 months. Our patient is unusual in continuing to survive 46 months after the original diagnosis. Instances of such long survival are rare (Rogoff *et al.*, 1973) as are pulmonary metastases (Winslow and Taylor, 1960; Elmes, 1972). Pleural effusion is recognized due to tumour growth through the diaphragm (Moertel, 1972; Kannerstein and Churg, 1977).

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Book reviews

Glucagon in Gastroenterology. The proceedings of an international workshop held in Madrid on May 31, 1978 under the auspices of the Medical School of the Universidad Complutense, Madrid. Edited by J. Picazo, pp. 146 (M.T.P. Press Ltd., Lancaster, England), £9·95.
ISBN 0-85200-254-8

This small book is an account of the papers and discussions, given at a one-day meeting in Madrid, of a number of experts from different disciplines who are interested in glucagon. This is a gastro-intestinal hormone, produced in the pancreatic alpha cells, which was discovered at about the same time as insulin but has attracted interest only comparatively recently. Those present included a group of leading workers in the fields of physiology, radiology, endoscopy, surgery and hepatology from many countries in Europe and from the United States.

The formal papers covered the pharmacological action of glucagon as a drug, the physiological role of glucagon in the gastro-intestinal tract, the use of glucagon in endoscopy, biliary surgery and in the treatment of hepatic failure. But the part of most interest to readers of this review will be the chapter devoted to glucagon in radiology, which was contributed by Dr. Louis Kreel who, for many years, has been advocating its use.

Dr. Kreel stressed that from the radiological point of view the main action was in diminishing the tone and motility of the stomach, duodenum, small bowel and colon, thus abolishing peristalsis and allowing full distension. He pointed out that it has no effect on oesophageal peristalsis but does relax the cardiac sphincter. It appears also to relax the smooth muscle of the ureter, bladder, gall-bladder and the sphincter of Oddi.

The outstanding impression gained from this chapter and from others is the comparative safety and lack of side effects of glucagon when administered intravenously in the doses necessary in radiological investigations. This appears to vary between 0.1 and 0.2 mg. At this dosage there appear to be virtually no contra-indications but when larger doses are administered the possibility of provoking reactive hypoglycaemia in patients with insulinoma, and hypertension in patients with pheochromocytoma must be considered. It is suggested that when the suprarenals are being investigated by computed tomography to exclude a pheochromocytoma it is advisable to use Buscopan rather than glucagon. The theoretical possibility that patients could develop a hypersensitivity reaction to repeated injections of a foreign protein has not, in the event, been a problem. Moreover, in the small doses required for double-contrast barium-meal examinations, glucagon is little more expensive than Buscopan and has fewer side effects, as well as other advantages.

This small but interesting book would repay study by anyone interested in the use of drugs in gastro-intestinal radiology.

L. W. LAWS.

Radiology of the Acute Abdomen in the Newborn. A Self-teaching Manual. By L. Cipel, pp. xv+294, 1978 (Grune and Stratton, Inc., New York), $32.50/£21·50.
ISBN 0-8089-1071-X

The author, drawing on a large clinical experience and an extensive review of the literature, has produced a self-teaching manual as an alternative to the ordinary type of textbook.

The book contains a series of diagnostic problems, essentially relating to the alimentary tract of the neonate, with radiographs and answers, descriptions of the conditions so illustrated and several quizzes. The author suggests varying methods of study depending upon the experience of the reader.

Cover of the subject matter is comprehensive from the simple and common to the obscure and difficult condition. References for further reading and lists of gamuts are included. Some of the films are not very easy to see clearly but neonatal films are difficult to reproduce. The author also gives his own technique of examination as a guide whilst appreciating that others may approach problems in a slightly different way

The book is entertaining and instructive, especially if used intermittently, and if the reader likes the format of self-evaluation and teaching programmes. It should, I feel, complement rather than supplant the standard texts.

D. SHAW.

1979, *British Journal of Radiology*, *52*, 1005

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

SI units and dimensions of NSD

THE EDITOR—SIR,

I think first it is questionable whether the "unit" of NSD—ret—should be so dignified. It is not a physical quantity but a biological effect and, as such, depends on factors the effect of which cannot at present be measured. The dimensions of rad are

$$\frac{ML^2T^{-2}}{M}$$

i.e. squared velocity or length times acceleration. The dimensions of ret are (rad$/T^{0.11}$), $L^2T^{-1.89}$. This is for a definite tolerance level which may vary from centre to centre and from one tissue to another.

The biological effect of radiation is of two types: 1, that on the normal tissues to which the NSD concept was meant to apply, and 2, that on tumour cells (TSD in ren). The difference between these effects is in the effect of homeostatic control to which the factor $T^{0.11}$ applies. Besides this, time-lapse allows of recovery by division of cells in both normal tissues and malignant tumours and, as said in the first publication about the NSD concept (Ellis, 1967), this type of recovery does not depend on the essential difference between normal and malignant cells and therefore does not enter into the NSD formula which was derived utilizing that difference. Instead, this type of recovery by cell-division, common to both types of cell, which is uncertain as to the time of its commencement and the rate at which it proceeds, is probably dependent on nutrition, cell-cycle time, oxygenation, temperature and other things so that a full equation should probably be

$$\text{Biological Effect} = \text{Dose (rad) Time}^x\, F^y$$

where F is an unknown and complex factor. The NSD concept being an attempt to separate fractionation from the effect of time in delivering the radiation was clearly a simplified and incomplete theory but its units are nevertheless more complex than those of the rad. On the other hand, the ren has the same dimensions as the rad. The TDF simplification of the NSD concept depends on the NSD formula and on the principle of proportional tolerance embodied in the NSD concept. For example, using the formula, 15 × 200 rad five times a week gives 1127 ret. Twice this is 2254 ret. On the other hand, 30 × 200 five times a week gives 1768 ret. Since the NSD represents a tolerance level, then in comparison with 30 fractions at the same rate 15 fractions is half the course and $\frac{1}{2}+\frac{1}{2}=1$.

To avoid confusion due to imperfect understanding of this proportional (or partial) tolerance principle, the Time Dose Fractionation modification was developed (Orton and Ellis, 1973). $\text{TDF}=10^{-3}nd^{1.538}x^{-0.169}$ where $x=T/N$. The TDF values for various schedules and parts of courses can be added in such a way as to represent similar effects even when adding the effects of fractionated and continuous radiation.

The "dimensions" of TDF are:

$$(L^2T^{-2})^{1.538}(T^{-0.169})$$

i.e. $L^{3.076}T^{-3.245}$—a difficult medical pill for the physicist to swallow.

Yours, etc.,
F. ELLIS.

The Old Bakery,
Thames Street,
Charlbury,
Oxford OX7 3QQ.

(*Received May 1979*)

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ORTON, C. G. and ELLIS, F., 1973. A simplification in the use of the NSD in practical radiotherapy. *British Journal of Radiology*, *46*, 529–537.

SI units and dimensions of NSD

THE EDITOR—SIR,

My recent letter on the above subject (Greening, 1978) has brought me correspondence from Dr. D. Bewley, Dr. M. Day and Dr. F. Ellis as a result of which I wish to make a small correction to my letter. I wrote:

"$D=\text{NSD}\ (t/t^{\theta})^y\ N^{0.24}$

where t is time and t^{θ} is a standard value of time.

When t^{θ} is equal to one day y takes the value 0.11."

It is this last sentence that is incorrect, as $y=0.11$ whatever the standard value of time chosen. I must hasten to add that this does not affect my argument about the dimensions of NSD or the SI units in which it should be expressed.

Yours, etc.,
J. R. GREENING.

The Department of Medical Physics and
Medical Engineering,
Royal Infirmary,
Edinburgh, EH3 9YW.

(*Received September 1979*)

REFERENCE

GREENING, J. R., 1978. SI units and dimensions of NSD, CRE and TDF. *British Journal of Radiology*, *51*, 1026.

Biliary rhabdomyosarcoma of childhood

THE EDITOR—SIR,

I read with interest the report by Cannon *et al.*, (1979) emphasizing the role of percutaneous transhepatic cholangiography (PTC) in the management of biliary rhabdomyosarcoma of childhood. While agreeing about the importance of early diagnosis of biliary obstruction and particularly of childhood rhabdomyosarcoma, I should like to emphasize the role of less invasive radiological procedures in the management of this rare tumour of childhood.

Recently I have seen two young children with rhabdomyosarcoma of the bile ducts. The first had hepatomegaly and had been jaundiced for six weeks when an ultrasound scan showed dilatation of the bile ducts and gall-bladder. Barium studies and PTC were then undertaken to help define the nature and the extent of the obstructing lesion prior to surgery. The appearances on PTC were similar to those described in the case reported by Cannon *et al.* (1979).

The second child had marked hepatic enlargement and had been jaundiced for ten weeks prior to ultrasound scan. This scan showed that the right lobe of the liver had been completely replaced by an enormous mass containing complex echoes resembling "swiss cheese", (Fig. 1). A technetium sulphur colloid scan showed that the mass was intrahepatic, a point not clearly shown on the ultrasound scan. This patient proceeded to subtotal hepatectomy

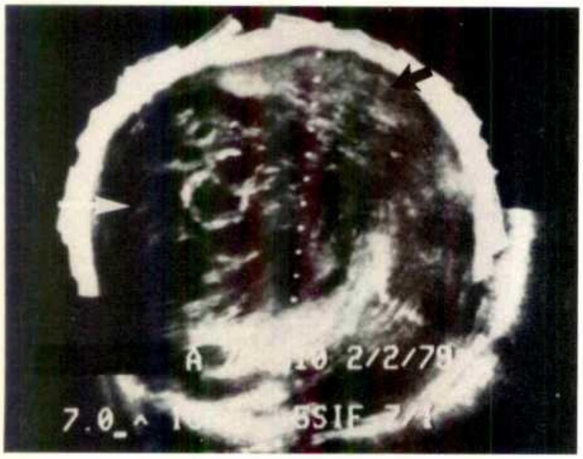

FIG. 1.

Transverse ultrasound scan of the abdomen 7.0 cm above the iliac crest. The mass containing complex echoes and replacing the right lobe of the liver is shown (white arrow), and normal parenchyma in the left lobe of the liver is also shown (black arrow).

without resort to PTC. Indeed had such a procedure been carried out prior to the ultrasound scan the cholangiography needle inevitably would have entered the tumour rather than the bile ducts.

Yours, etc.,
J. B. WITCOMBE.

The Department of Diagnostic Radiology,
The Medical School,
Oxford Road,
Manchester M13 9PT.

(*Received February 1979*)

REFERENCE

CANNON, P. M., LEGGE, D. A. and O'DONNELL, B., 1979. The use of percutaneous transhepatic cholangiography in a case of embryonal rhabdomyosarcoma. *British Journal of Radiology*, *52*, 326–327.

Anaesthesia and efficacy of hyperbaric oxygen in radiation therapy

THE EDITOR—SIR,

The data presented by Suit *et al.* in their recent letter (1979) demonstrate one effect that nembutal anaesthesia can have on the radiation response of tumours. Their results are in agreement with our findings from a number of years ago (Milne *et al.*, 1973) that in comparison to no anaesthesia both nembutal and urethane improved oxygenation in the KHT sarcoma when the host animal breathed oxygen at 200 kPa (HPO), with urethane giving a greater improvement than nembutal. This result may be considered somewhat surprising since barbiturates affect the heart and respiration rates of mice and reduce peripheral blood flow and body temperature (Kruuv *et al.*, 1967; Johnson *et al.*, 1976), factors which could lead to a reduction in tumour oxygenation. Indeed we have results (unpublished) indicating that in air-breathing animals anaesthesia with nembutal and, to a smaller extent, urethane can reduce the radiation response of the KHT sarcoma probably as a result of changes in tumour oxygenation. Sheldon *et al.* (1977) have also shown that nembutal anaesthesia protects the "MT" mouse tumour against radiation damage although in their case protection was greater than could be explained by changes in tumour oxygenation alone. Conversely Suit *et al.* (1972) found no effect of nembutal anaesthesia when studying a mammary tumour irradiated in air-breathing mice although this may have been because they used a ten-fraction regime.

We proposed (Milne *et al.*, 1973) that one explanation for the anomalous effect of anaesthesia during HPO breathing could be that the anaesthesia prevented, wholly or partially, the vasoconstriction which can result from HPO breathing. The difference between the two anaesthetics observed in our experiments could then be explained by the other physiological parameters discussed above which change to a much greater extent following anaesthesia with nembutal than urethane. Suit *et al.* (1979) suggest in their letter that the vasoconstriction hypothesis is unlikely to explain their results because they found an enhancement factor (TCD_{50} air/TCD_{50} HPO) of only 1.1 for single dose irradiation under nembutal anaesthesia. We think that this small effect is probably due to the other confounding factors mentioned above and that vasoconstriction and its inhibition by anaesthesia is the major reason for the difference between the results for animals breathing air or HPO.

We would agree with Suit *et al.* (1979) that the clinical experience with HPO may well have been adversely affected by the change from anaesthetized to non-anaesthetized patients, but our results indicate that, because of the interacting physiological factors discussed above, barbiturates are unlikely to be the most appropriate choice for any new study of the role of anaesthesia in the clinical combination of HPO and radiation therapy.

Yours, etc.,
R. P. HILL,
R. S. BUSH.

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(*Received May 1979*)

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Proceedings of The British Institute of Radiology

Annual Congress Scientific Exhibition, April 26–27, 1979

Assessment of scoliosis in children—low dose radiographic technique, by G. M. Ardran, R. Coates, R. A. Dickson, A. Dixon-Brown and F. M. Harding.
Contemporary cardiac calcification, by A. Arocha, T. J. Bloomberg and T. J. Terry.
The double contrast barium enema. Construct a stable film holder in the hospital workshop, by G. de Lacey, Ann Paris, D. Sanders, B. Wignall, Moira Kirk, B. Barry and D. Soutar.
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Necrotizing enterocolitis—a radiological/pathological correlation, by J. Virjee and G. Stevenson.
A prototype microprocessor-based treatment control console for linear accelerators, by I. C. P. Millar.
Total body irradiation before bone-marrow grafting in acute leukaemia, by Ann Barrett, P. A. Hickling, Gillian P. Lawrence and M. E. Rosenbloom.
The cytotoxic action of adriamycin on mouse tumours, by W. M. C. Martin and N. J. McNally.
Measurement of the performance characteristics of diagnostic X-ray systems used in medicine, by B. Baily.
Reduction of radiation dose to the patient in xeromammography by added filtration, by A. M. Baker, R. Davis, D. R. Dance and C. A. Parsons.
Survey of mammography in Britain, by M. Fitzgerald and D. R. White.
Radiographic anatomy and load bearing characteristics of the foot in hallus valgus, by A. J. Ward, B. S. Worthington and F. Johnson.
Non-movement artefacts in computed tomography, by Brenda M. Sandin
The Cleon single-photon emission CAT System, by M. A. Flower, I. P. Coles, R. P. Parker, N. G. Trott, S. Meller and V. R. McCready.
Ultrasound demonstration of normal and abnormal fetal anatomy, by Pat Farrant and H. B. Meire.
Non-invasive arteriography by pulsed Doppler ultrasound, by C. A. Wood and H. B. Meire.

ASSESSMENT OF SCOLIOSIS IN CHILDREN—LOW DOSE RADIOGRAPHIC TECHNIQUE

By G. M. Ardran, R. Coates, R. A. Dickson, A. Dixon-Brown and F. M. Harding

Nuffield Orthopaedic Centre, Department of Radiology, University of Oxford and Department of Radiation Physics, Churchill Hospital, Oxford

When scoliosis is first clinically suspected a child may need an erect radiograph of the whole spine to confirm the presence of scoliosis, to assess its degree and to detect gross congenital defects.

Radiographs are usually taken in the AP projection with an anti-scatter grid. Films are exposed using an air gap technique similar to that used for chest radiographs, to obviate the extra exposure required when using a grid. The use of a 15 cm air gap, a 365 cm focus film distance and DuPont Quanta II intensifying screens has produced satisfactory results. This reduces the skin dose by a factor of about four compared with the grid technique: on average, in children age 9 to 14 years, from 0.96 mGy to 0.19 mGy. The use of the PA rather than the AP projection considerably reduces the breast dose from 0.96 mGy to 0.016 mGy. 1 mGy = 100 mrad.

CONTEMPORARY CARDIAC CALCIFICATION

By A. Arocha, T. J. Bloomberg and T. J. Terry

National Heart Hospital

Calcification is a frequent finding on radiographs of patients with heart disease. Examples of calcification in classical situations such as aortic and mitral valves, as well as in the less common positions of the left atrium, the pericardium, a left ventricular aneurysm and the coronary arteries, are shown.

Patients with surgically corrected congenital heart disease may also show calcification in different situations, and examples are shown of (a) calcification in a homograft aortic valve replacement of the pulmonary valve in a patient with the tetralogy of Fallot; (b) calcification in a conduit between the right atrial appendage and the pulmonary artery, in tricuspid atresia and (c) calcification in a right ventricular outflow tract aneurysm which developed in a patient with the tetralogy of Fallot, in whom there was inadequate relief of the pulmonary valve stenosis.

THE DOUBLE CONTRAST BARIUM ENEMA. CONSTRUCT A STABLE FILM HOLDER IN THE HOSPITAL WORKSHOP

By G. de Lacey, Ann Paris, D. Sanders

Northwick Park Hospital and the Clinical Research Centre, Harrow, Middlesex

B. Wignall, Moira Kirk

St. George's Hospital, London

B. Barry and D. Soutar

Sydney, N.S.W., Australia

A previous study had shown that on 200 lateral decubitus views from 100 double contrast barium enemas there was unacceptable unilateral under or over penetration on 67% of the films (de Lacey *et al.*, 1978). In most cases this was due to grid cut-off caused by an unstable cassette—usually propped up in the Bucky or with sand bags. This exhibit demonstrated three different types of stable lateral film holder, each of which may be constructed in a Hospital Workshop. One design was for a table with a side bar, another was for a table with a grooved top, and the third holder was mobile on wheels.

REFERENCE

de Lacey, G., Wignall, B., Ambrose, J., Baylis, K., and Bridges, C., 1978. The double contrast barium enema: improvements to lateral decubitus views including the use of a wedged filter. *Clinical Radiology*, *29*, 197–199.

THE TWISTED ANKLE. X RAYS INDICATE THE MECHANISM OF INJURY

By G. de Lacey, R. Mitchell

X-ray Department, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex

and Shirley Bradbrooke

X-ray Department, St. George's Hospital, London

Fractures at the ankle joint may be classified as Potts fractures, but this is often a confusing and unhelpful description. Ankle fractures are better classified according to the causative force, and the mechanism of injury whether inversion, external rotation or eversion, can be determined in the majority of cases from the X-ray appearance of the fracture. It is the appearance of the fibular fracture that is the key to the mechanism. The appearance of the medial malleolar fracture, when present, will help confirm the mechanism of injury. Avulsion of the tip of the lateral malleolus or a low transverse fracture of the fibula suggests an inversion injury; a spiral fracture of the lateral malleolus indicates an external rotation injury; and a fracture of the fibula just above the inferior tibio-fibular ligament indicates an eversion injury.

A DETACHABLE BALLOON TECHNIQUE FOR THE TREATMENT OF ANEURYSMS AND FISTULAE OF THE INTERNAL CAROTID ARTERY

By T. D. Hawkins and S. M. Crinson

Department of Diagnostic Radiology,
Addenbrooke's Hospital,
Hills Road, Cambridge CB2 2QQ

The orthodox surgical treatment of large aneurysms of the cavernous and supraclinoid segment of the internal carotid artery and of the carotico-cavernous fistulae is not always successful. An endarterial approach using a detachable balloon catheter is an alternative and potentially more effective treatment.

The catheter assembly used to treat these lesions was described and illustrated followed by a detailed description of the balloon occlusion procedure.

Some of the patients with carotid aneurysms and fistulae successfully treated by this technique were described and illustrated by angiograms, clinical photographs and computerized axial tomograms.

A table of the results of cases treated by this method was shown and supplementing the exhibit was a videotape recording of several balloon occlusion procedures.

A sample of the balloons and catheters used was on display.

MEASUREMENT OF LUNG VOLUME FROM CHEST RADIOGRAPHS

By R. Pierce, D. Brown, D. Denison and I. Kerr

Brompton Hospital, London

Accurate estimates of lung volume may be made from standard PA and lateral chest radiographs. The method is based on an assessment of the cross-sectional shape of the chest and its contained structures obtained from post-mortem anatomical studies and computerized tomography of the living chest (Pierce *et al.* 1978). The outlines of each structure are digitized and fed into a computer which aligns the PA and lateral images, divides them into many horizontal slices and determines the cross-sectional area and then volume of each structure in each slice from its two linear diameters using simple shape equations. Summing the slices gives the total volume of each structure and subtraction of the heart, spine and subphrenic volumes from the chest volume gives the displacement volume of the lungs. Studies in normal and asthmatic subjects showed good correlation between radiographic displacement volume, plethysmographic total gas volume and helium-dilution accessible gas volume of the lungs. The method has been extended to measure the volume of individual lobes and segments and of lung lesions (Pierce *et al.*, 1979; Williams *et al.*, 1979). Volumes may also be estimated from radio-isotopic scintigrams of lungs or lobes. These methods are useful in the functional assessment of generalized and focal lung disease.

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RADIOLOGY AND THE SPATIAL FREQUENCY MODEL OF VISION

By B. S. Worthington and A. Gale

Academic Department of Radiology,
University of Nottingham

To assess the ability of a lens to reproduce both fine and coarse detail at different contrasts a grating is used whose light and dark bars have a sinusoidal variation in intensity. The number of bars or cycles subtended in each degree of arc is a measure of the fineness of detail called the spatial frequency, Campbell and Robson (1968) have used similar test objects to measure the contrast sensitivity of the visual system at different spatial frequencies. This shows its highest sensitivity to low contrast at three cycles/degree and a response up to 50 cycles/degree but only at high contrast. There is evidence that the visual system contains several channels each tuned to a narrow band of spatial frequencies. Magnification of an image shifts the sensitivity curve of the eye in the spatial frequency domain by the amount of the magnification. Altered viewing distance can ensure the best match in the spatial frequency domain between low contrast detail of a given size and the performance capabilities of the visual system. Spatial frequency filtration of CAT scans removes high-frequency grain noise which can mask important detail. Harmonization enhances the contrast of fine detail elements in an image and, therefore, improves their perceptibility.

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CAMPBELL, F. W. and ROBSON, J. G., 1968. Application of Fourier analysis to the visibility of gratings. *Journal of Physiology*, *197*, 551–556.

NECROTIZING ENTEROCOLITIS—A RADIOLOGICAL/PATHOLOGICAL CORRELATION

By J. Virjee

Bristol Royal Infirmary

and G. Stevenson

McMaster Medical Centre

Necrotizing enterocolitis is a clinical syndrome primarily occurring in premature low birthweight infants.

The exhibit indicates the pathogenetic mechanism in the development of this disease with radiological and pathological (both macroscopic and histological) correlative demonstrations of each stage of the primary disease and its subsequent complications (both early and late).

The incidence of these complications—especially the late complications (stricture, atresia, enteric cyst, malabsorption, internal fistula) which have been previously rarely encountered—is increasing due to the higher survival rate of this once usually fatal condition.

A PROTOTYPE MICROPROCESSOR-BASED TREATMENT CONTROL CONSOLE FOR LINEAR ACCELERATORS

By I. C. P. Millar

Particle Accelerator Division,
M.E.L., Manor Royal, Crawley, Sussex

A microprocessor-based control console has been constructed for SL75-14 and SL75-20 linear accelerators. The new console gives improved control and more information is shown with greater clarity. Traditional knobs, switches and meters have been superseded by a microprocessor-controlled video display unit and alpha-numeric keyboard.

The new control console is programmed to lead the operator through the setting-up procedure by information supplied on the screen. Any settings which are inconsistent with the type of treatment or with selections made inside the treatment room are highlighted on the screen and operation is inhibited until a correction has been made. The system incorporates fully independent dual-channel dosimetry, a back-up timer and other safety features pioneered by Philips.

Interfaces are available to connect the new control console to Philips automatic treatment verification and recording equipment and to external computers for further automation.

TOTAL BODY IRRADIATION BEFORE BONE-MARROW GRAFTING IN ACUTE LEUKAEMIA

By Ann Barrett, P. A. Hickling,
Gillian P. Lawrence, and M. E. Rosenbloom

Radiotherapy and Physics Departments,
Royal Marsden Hospital and Institute of Cancer Research,
Downs Road, Sutton, Surrey

Total body irradiation is now used routinely at the Royal Marsden Hospital in the preparation of patients about to receive a bone-marrow transplant in the treatment of acute leukaemia. The exhibit summarizes the clinical results of a period of two years. It also demonstrates the principles of the technique and some physical measurements. The patient is treated using cobalt γ rays with an SSD of 4 m. Six treatment positions are used to optimize dose distribution. A Perspex cot is used to help the patients maintain their position throughout the treatment which lasts approximately six hours. Dosimetry is based on thermoluminescence using a large number of dosimeters placed on the patient's skin.

THE CYTOTOXIC ACTION OF ADRIAMYCIN ON MOUSE TUMOURS

By W. M. C. Martin and N. J. McNally

Gray Laboratory, Mount Vernon Hospital,
Northwood, Middlesex

Mouse tumour lines which can be grown *in vivo* as subcutaneous tumours, or as lung metastases, or *in vitro* in monolayer or Spinner cultures, were used. Adriamycin is a highly effective cytotoxic agent *in vitro* on each of the two tumour lines, WHFIB and CBSAF. Survival curves were biphasic for WHFIB cells, as given by $D_0 = 0.11$ μg/ml for the sensitive phase, $D_0 = 6$ μg/ml for the resistant phase. The resistance seen in the tail was not inherited since cells surviving a high dose again showed a biphasic survival curve.

Tumours *in vivo* were very resistant to the drug. Assayed *in vitro* survival was never less than 30% at a dose of the LD50, 18 mg/kg given IP or IV. Survival was still as high at this dose in 2 mm lung metastases. Divided doses spaced six to eight hours apart also did not reduce survival.

Why the marked difference between *in vitro* and *in vivo* sensitivity? Drug levels adequate to reduce survival by over three decades were measured in tumours, using a fluorometric method. Cell suspensions were more sensitive under oxic than hypoxic conditions. This was insufficient to explain the resistance of cells in tumours. Cells in plateau phase in Spinner culture were much more resistant to adriamycin than cells in log phase. Thus, a large number of cells out of cycle could explain the resistance of cells in tumours.

MEASUREMENT OF THE PERFORMANCE CHARACTERISTICS OF DIAGNOSTIC X-RAY SYSTEMS USED IN MEDICINE

By B. Baily

Diagnostic Radiology Topic Group,
Hospital Physicists' Association

The Diagnostic Radiology Topic Group is preparing five protocols for the performance testing of medical diagnostic X-ray systems: X-ray tubes and generators; X-ray image intensifier television systems; Processors, films and screens and tomographic systems; 'Computerized Tomography'.

The exhibit illustrates the results obtained from application of Parts I and II, X-ray tubes and generators and X-ray image intensifier television systems, particularly in respect of the variations found from unit to unit.

Most of the equipment required for carrying out the tests is on display and includes a new multi-cassette Ardan-Crookes penetrameter. The testing of image intensifier systems is perhaps less well standardized and the Leeds test objects used in the visual assessment section of Part II are on view, with a brief description of their use.

Dynamic testing has been little explored, particularly in relation to cine and 70/100 mm indirect radiography. It is intended that this should form a section of Part II and an experimental test object is on display.

REDUCTION OF RADIATION DOSE TO THE PATIENT IN XEROMAMMOGRAPHY BY ADDED FILTRATION

By A. M. Baker, R. Davis, D. R. Dance and C. A. Parsons

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The addition of aluminium filtration to a mammographic X-ray beam can reduce the softer components of the beam that contribute to absorbed dose without providing useful information in the image. To investigate the effect of added filtration on mammograms a clinical trial was carried out on selected patients using molybdenum or tungsten anode tubes, and positive or negative mode development. It was established that mammograms of the same diagnostic value as those obtained with unfiltered beams could be achieved for up to 3.5 and 2.5 mm Al total filtration for negative and positive development respectively using the tungsten anode tube and for 1.6 mm Al total filtration using the molybdenum anode tube.

Measured skin exposures were related to absorbed dose in the breast by Monte Carlo computation using X-ray spectra matched to our measured half-value layers and tube potentials. The exposure reduction factor achieved by adding filtration ranged from 1.7 to 2.9 with a corresponding reduction in energy absorbed of 1.3 to 2.2.

The work was illustrated by mammograms taken with and without additional filtration and by figures showing the results of exposure measurement and absorbed dose calculation.

SURVEY OF MAMMOGRAPHY IN BRITAIN

By M. Fitzgerald and D. R. White

Department of Radiation Physics, St. Bartholomew's Hospital, London

This exhibit featured some of the information and results obtained from a survey proposed by the Hospital Physicists' Association. At each of the 61 centres visited, X-ray beam characteristics and average patient doses were measured; image quality was assessed from the images of a phantom by physicists and radiologists using a scoring method. The mammography techniques encountered varied greatly and various aspects were presented. Absorbed doses were calculated at the surface of an average-sized, 5 cm thick, 50% fat/50% water, homogenous breast for single cranio-caudal (c-c) and medio-lateral (m-l) views and they showed a wide range. The results fell naturally into the four combinations of molybdenum (Mo) and tungsten (W) targets and film (F) and xerox (X) receptors. The Mo/X group produced the highest mean image score but also the highest mean dose (c-c: 3.26 cGy (rad), m-l: 3.39 cGy (rad)) and its use seems justified only for symptomatic diagnosis. For non-symptomatic screening the Mo/Lo-dose or MIN-R film (LMF) and W/X groups offered good results; mean surface doses for the c-c and m-l views were respectively 0.95 and 1.07 cGy (rad) for the Mo/LMF group and 0.89 and 0.94 cGy (rad) for the W/X group which gave a 19% higher image score. The W/F group produced the poorest score and its use for mammography should be abandoned.

RADIOGRAPHIC ANATOMY AND LOAD BEARING CHARACTERISTICS OF THE FOOT IN HALLUX VALGUS

By A. J. Ward, B. S. Worthington and F. Johnson

Academic Department of Radiology, University of Nottingham

During standing the skeleton of the foot can be regarded as a plate deformed by the presence of a medial longitudinal arch and a series of transverse arches. In hallux valgus there is an untwisting and flattening of the plate as shown by a medial tilt of the talus and a flattening of the medial longitudinal arch. With progressing deformity there is a widening of the forefoot and force plate studies show a corresponding medial displacement of the locus of the centre of force which indicates an increase in the relative loading of the medial forefoot. Features which may predispose to hallux valgus include a relatively long first metatarsal; a relatively long hallux; a first metatarsal with a high pitch and a high medial longitudinal arch. The effect of footwear on the load-bearing pattern of the foot is to increase medial forefoot loading, this being progressive as heel height is raised. Six months after operation, despite anatomical correction of the deformity and relief of metatarsalgia, most patients still have a disturbed gait which is reflected in a persisting abnormal load-bearing pattern. An extended follow-up is in progress to determine whether, with suitable re-education, the load-bearing pattern can be altered for the better.

NON-MOVEMENT ARTEFACTS IN COMPUTED TOMOGRAPHY

By Brenda M. Sandin

Clinical Research Centre, Division of Radiology, Watford Road, Harrow, Middlesex

An array of water-filled polyethylene bottles was scanned with a CT 5005 whole-body scanner in order to study factors of importance in the production of linear artefacts similar to those found in clinical practice.

Detector misalignment produced artefacts in the stop-start axis of the scanner. These could be virtually abolished with correct alignment, but correct alignment for one direction of rotation was usually incorrect for the opposite direction and correct alignment for the 240 mm ring was usually incorrect for the 320 mm ring.

Excessive photomultiplier (PM) gain produced a set of intersecting lines across the central bottle. The addition of bolus material produced little change in artefact due to detector misalignment, but usually reduced that due to excessive PM gain.

Changes in kilovoltage, scan speed and object size did not in themselves predispose to artefact production, providing the PM gain was adjusted appropriately.

The linear artefacts produced only a small change in mean attenuation values. Greater variation was seen between the apparently artefact-free surrounding bottles, though these differences were reduced when an experimental reconstruction programme was used.

THE CLEON SINGLE-PHOTON EMISSION CAT SYSTEM

By M. A. Flower, I. P. Coles, R. P. Parker,
N. G. Trott, S. Meller and V. R. McCready

Physics and Nuclear Medicine Departments, The Royal Marsden Hospital and Institute of Cancer Research, Sutton, Surrey

The Cleon radionuclide brain imager consists of 12 detectors with focusing collimators which each perform a rectilinear scan within the plane of the transverse section. The mechanical movements which accomplish this complex motion were described and illustrated with a five minute film. A filtered projection method is used to reconstruct the raw data and different stages of the data manipulation for two radioactive sources were shown to illustrate the method. Four different resolution phantoms containing high concentrations of ^{99}Tc^{m} illustrated the resolution capabilities of the machine and five clinical case reports showed that emission tomography has a useful role to play in tumour localization.

ULTRASOUND DEMONSTRATION OF NORMAL AND ABNORMAL FETAL ANATOMY

By Pat Farrant and H. B. Meire

Northwick Park Hospital, Harrow, Middlesex

Ultrasound has been used for several years to visualize gross fetal anatomy; but with the use of modern technology high resolution grey scale pictures may be obtained, enabling fetal structure to be studied in detail.

The fetal head and body may be seen as two definitive structures by 11–12 weeks, thereby excluding the presence of anencephaly. At 15–16 weeks the spinal canal may be well seen, and by 20 weeks spina bifida, if present, should have been picked up. Examples of acrania, anencephaly and spina bifida are shown, together with normal spines and intracranial structures.

Soft tissue organs such as the spleen and kidneys may be scanned to confirm their presence, and two examples of hydronephrosis are shown, one mild and the other gross. With a good knowledge of normal fetal anatomy, it is possible to distinguish abnormalities such as those produced in rhesus isoimmunization where fetal ascites and oedema may be present, as well as hepatosplenomegaly.

NON-INVASIVE ARTERIOGRAPHY BY PULSED DOPPLER ULTRASOUND

By C. Wood and H. B. Meire

Clinical Research Centre,
Watford Road, Harrow, Middlesex

An exhibit is presented demonstrating some of the vessel imaging capabilities of a pulsed Doppler ultrasound machine —MAVIS (Mobile Artery and Vein Imaging System). This pulsed range-gated system uses a five megahertz probe connected to position sensors allowing a blood flow image shaped by the anatomy of the section of vessel insonated to be placed on an oscilloscope screen. The machine is sensitive to the direction of blood flow, and can produce images in antero-posterior, lateral and cross-sectional planes. The image and the local flow velocity data allow an estimate of the degree of patency of the vessel lumen at the point of examination. In addition conclusions can be drawn on the state of the vessel proximal and distal to the insonated segment.

Images of carotid, common femoral and popliteal artery bifurcations and the major groin veins illustrating the machine's ability to discriminate between normal, partially stenosed and occluded vessels are demonstrated. Images of the subclavian artery and origin of the vertebral artery in the root of the neck are shown, including a patient with subclavian steal syndrome with reversal of vertebral flow direction on the velocity waveform recording. These capabilities allow use of MAVIS in studies of deep vein thrombosis and vascular disease.

Forthcoming events and other notices

The editors have decided to accept requests for meeting announcements by organizations other than The British Institute of Radiology and its associated bodies on the basis of charging at £1·00 per line per edition. Copy deadline for inclusion in this section is the 20th of the penultimate month preceding publication (*i.e.* April 20, for June edition).

Requests should be addressed to Mrs. L. Surry, Managing Editor, The British Journal of Radiology, 32 Welbeck Street, London W1M 7PG.

Personal Exchanges in Cancer Research

The UICC wishes to bring to the attention of workers in cancer research the fact that funds are available to finance visits to centres abroad for periods up to 28 days. The purpose of the visit must be the transfer of information about new or improved techniques or methods between investigators in different countries. Grants can also be made towards the organization of small meetings of up to 12 investigators for a period not exceeding four days.

Further information can be obtained from UICC, Conseil-Général 3, 1205 Genève, Switzerland.

The Rationale for Unorthodox Fractionation

This review-type radiobiology meeting will be held in the Institute on Saturday, December 8, 1979. Speakers will be Fowler, Kirk, Hopewell, Svoboda, Dutreix. All are welcome.

Future radiobiology Work-in-Progress meetings will be a general meeting on February 15, 1980, and "Biological effects of doses below 2 Gray" on May 16, 1980

The British Medical Ultrasound Society
11th Annual Scientific Meeting

To be held on December 17–18, 1979 in Edinburgh.

Address for enquiries: Dr. W. N. McDicken, Department of Medical Physics and Medical Engineering, The Royal Infirmary, Edinburgh EH3 9YW.

Radiation Biology for Part I F.R.C.R. (Radiotherapy and Oncology)

An intensive course in Radiation Biology will be held at the Paterson Laboratories from January 21–25, 1980, inclusive. It is primarily intended for radiotherapists in training but is it also open to other students of radiation biology and experimental oncology. Lectures and demonstrations will be given by the staff of the Paterson Laboratories.

Enquiries should be addressed to Dr. J. H. Hendry, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX.

Modern Gastrointestinal Radiologic Techniques for the Practising Physician

San Francisco, January 26–27, 1980.

For further information contact: Radiology Postgraduate Education Section Room M396, University of California, San Francisco, California 94143 or call (415) 666–5731.

Radiology in the 1980s

A seminar critically appraising the use of imaging techniques will be held in the Clinical Research Centre, Harrow, on February 28–29, 1980. Early registration is recommended as the number of participants will be limited. Details from Dr. G. de Lacey, Northwick Park Hospital, Watford Road, Harrow, Middx. HA1 3VT.

Whither Neuroradiology?

An evening meeting to be held on January 18, 1980, organized jointly with the Royal Society of Medicine (Section of Radiology), The British Institute of Radiology and The Royal College of Radiologists. Speakers will include Prof. I. Sherwood, Drs. I. F. Moseley, B. S. Worthington, I. G. Wylie and K. J. Zilkha.

Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01-935 6237).

Cell and Protein Labelling with Gamma Emitting Radionuclides for *In Vivo* Studies

A meeting to be held on February 13, 1979 organized by the Nuclear Medicine Committee of The British Institute of Radiology, at Middlesex Hospital Medical School, London.

Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01-935 6237).

Investigative Laparotomy in Hodgkins Disease

A joint meeting of The British Institute of Radiology, the Royal Society of Medicine (Section of Radiology) and The Royal College of Radiologists to be held on February 15, 1980, organized by and held at the Royal Society of Medicine, London.

Prostate Cancer

The Royal College of Radiologists will be holding its second multidisciplinary clinical oncology symposium on February 22–23, 1980 at 66 Portland Place, London W.1.

It is intended for senior registrars, consultants and research workers, and selected topics on the subject of prostate cancer will be reviewed by authoritative speakers from the United Kingdom. The registration fee is £25.

Full details from the Meetings Secretary, The Royal College of Radiologists, 38 Portland Place, London W1N 3DG.

The Fleischner Society Tenth Annual Symposium on the Chest

The Fleischner Society, a multidisciplinary international organization devoted to the study of the chest, announces its annual postgraduate course on major problems and important topics in chest disease, anatomy, physiology and clinical medicine with emphasis on radiolocis techniques and interpretation. Three days of fully accredited teaching, Monday–Wednesday, February 25–27, 1980, at the recently opened New Orleans Hilton Hotel. Lectures, a large selection of refresher courses, and both scientific and technical exhibits will be presented. The fee is $300 ($150 for certified residents and fellows) payable to the Fleischner Society. Meeting Manager: Robert Fraser.

For registration and information write to: Ms Jan Carr, New Orleans Convention Center, 2621 Prytania Street, New Orleans, Louisiana 70130. Tel. (504) 891 9965 or 899 2209.

Sierra Radiology Conference

The Sierra Radiology Conference covering Radiology of Problems in Clinical Medicine and sponsored by the Sacramento Radiology Research and Education Foundation and The Northern California Radiological Society will be held at South Lake Tahoe, Nevada on February 27–29,

1980. Speakers will include Drs. Henry Goldberg, Timothy Lee, David Merten, Maurice Reeder (guests) and the radiology faculty of the University of California, Davis.

An algorithmic approach to the radiological evaluation of clinical disease will be stressed. The fee is $215 or $150 for residents and fellows and the programme offers 18 hours of approved Category 1 AMA credit.

For further information, contact Michael H. Reid, M.D., Ph.D., Programme Director, Sacramento Radiology Research and Education Foundation, P.O. Box 161112, Sacramento, California 95816, USA.

THIRD ANNUAL REFRESHER COURSE

The Society of Computed Body Tomography will offer its Third Annual Refresher Course, March 2–6, 1980 at the Del Coronado Hotel, San Diego, California. The course will include an assessment of "state of the art", 2–5 second CT body scanners, dynamic CT scanning, new insights into thoracic and abdominal anatomy as seen with CT, and CT-guides interventional techniques. The relationship of CT to other imaging methods, including ultrasound, nuclear medicine and angiography will be emphasized. The faculty will include Drs. Alfidi, deWinter, Doppman, Evens, Glenn, Goldberg, Haaga, Harrel, Hattery, Kazam, Korobkin, Kreel, Sagel, Sample, Schellinger, Sheedy, Stanley, Stephens and Wittenberg. The fee is $250.

For further information write to Robert J. Stanley, M.D., Mallinckrodt Institute of Radiology, 510 South Kingshighway, St. Louis, MO 63110, USA.

5TH INTERNATIONAL CONGRESS OF THE INTERNATIONAL RADIATION PROTECTION ASSOCIATION

Will take place in Jerusalem, Israel, March 9–14, 1980.

The scientific programme of the Congress will cover all aspects of radiation protection with emphasis on its central theme: radiation protection—a systematic approach to safety.

An interesting programme has been planned including a commercial exhibition and pre- or post-congress workshops and professional tours.

Social events and a programme for accompanying persons have been organized.

For further information: The Secretariat, 5th International Congress of IRPA., PO Box 16271, Tel Aviv, Israel.

EORTC SYMPOSIUM ON IMMUNOPHARMACOLOGIC EFFECTS OF RADIOTHERAPY

Montpellier, France, March 13–15, 1980.

The programme will include invited and proferred papers.

The meeting is designed to promote discussions on the following topics: Effects of ionizing radiation on the immune response; clinical and experimental aspects. Immediate, secondary and long term incidences of the radiotherapy on the immune response and on the host tumour relationship in cancer patients. Correction or modulation of the changes induced by radiotherapy. Therapeutical associations: radiotherapy—immunotherapy; radiotherapy—chemotherapy; immunotherapy: experimental protocols, clinical trials and on-going studies.

Free papers will be submitted to the Scientific Committee.

The proceedings and reports from invited speakers will be published.

Abstracts, subscription and registration fees (600 FF/$140) are to be sent not later than February 15, 1980 to the General Secretary.

The number of inscriptions will be limited to 100.

Organizing Committee: Dr. J. B. Dubois (Montpellier), Dr. B. Serrou (Montpellier), Dr. C. Rosenfeld (Villejuif).

Further information can be obtained from Dr. J. B. Dubois, General Secretary, Centre Paul Lamarque, Hôpital Saint Eloi, B.P. 5054, Montpellier, France.

B.I.R. ANNUAL CONGRESS 1980 AND SCIENTIFIC EXHIBITION

The British Institute of Radiology Annual Congress will be held on April 17–18, 1980 at the Royal Free Hospital and will include the Sylvanus Thompson Memorial Lecture, presented by Sir Richard Doll.

Further information from the General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG (01–935 6237).

SYMPOSIUM ON SPINE AND ITS CONTENTS

EAR "Symposium Vertebrologicum" (Spine and its Contents) will be held from April 23–25, 1980 in Prague, Czechoslovakia.

The subjects of this symposium will be recent advances and experiences in:

(a) Equipments and investigative methods of spine and spinal cord.
(b) Radioanatomy and physiology of spine and spinal cord.
(c) Radiodiagnosis of pathological conditions.
(d) Interventive (diapeutic) radiodiagnostic methods.

For further information contact The secretariat of "Vertebro 1980", PO Box 88, Sokolská 31, 120 26 Praha 2, Czechoslovakia.

EUROPEAN SYMPOSIUM ON LUNG CANCER (EAR)

The symposium, organized by the Greek Radiological Society under the auspices of the European Association of Radiology will be held September 7–13, 1980 at Chalkidiki, Greece.

For further information contact the Secretariate, Department of Radiology, Areteion Hospital, 76 Vass. Sofias, Athens, Greece.

MEASUREMENT STANDARDS IN RESPECT OF BOTH IONIZING AND NON-IONIZING RADIATION HAZARDS

An all day meeting with the National Physical Laboratory and The British Institute of Radiology is to be held on May 14, 1980 at the NPL, Teddington, Middlesex.

XV INTERNATIONAL CONGRESS OF RADIOLOGY

The XV International Congress of Radiology will take place June 24–July 1, 1981 in Brussels, Belgium.

The scientific activities of the Congress as well as the scientific and technical exhibitions will take place in the Brussels Exhibition Centre.

Further information from: Secretariat ICR-81, Ave. Winston Churchill 234B-Box 16, B-1180 Brussels, Belgium.

TENTH L. H. GRAY CONFERENCE

Will be held in Oxford on July 13–16, 1981 on "biological actions of radiofrequency, microwave and ultrasonic radiations".

A conference to review and discuss past and current research on the radiobiology and biophysics of the radiations, particularly in relation to their potential therapeutic value.

Information/Chairman of Organizing Committee: Dr. C. R. Hill, Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey.

Membership Subscription Reminder

Members of The British Institute of Radiology are reminded that new membership subscription rates become due on January 1, 1980, as follows:

Ordinary Member (UK)	£20·00
Ordinary Member (outside UK)	£17·00

Members in training and radiographers pay reduced rates.

Cheques should be made payable to The British Institute of Radiology, crossed and sent to the General Secretary, BIR, 32 Welbeck Street, London W1M 7PG.

Book reviews

Röntgenologische Differentialdiagnostik. Band II. Erkrankungen der Bauchorgane. By D. W. Teschendorf and W. Wenz, pp. xvi + 640, 1978 (Thieme, Stuttgart) DM. 288.
ISBN 313–4571–05–6

This book of 638 pages aims to discuss the radiological differential diagnosis of the abdominal contents; accordingly there are chapters on the plain abdomen, the alimentary tract, the renal system, gall bladder, suprarenal glands, liver, spleen, pancreas and retroperitoneal structures. Normal radiological anatomy is discussed in each chapter and there then follows a discussion of the possible methods of investigation. Ultrasound, scintiscanning and CT scanning are discussed cursorily, but not illustrated. Arteriographic findings are well illustrated and discussed. There are good lists of differential diagnoses. The illustrations are all of outstanding quality and the book is attractively produced. The general level of discussion is good but the sections on the gastro-intestinal tract are exceptional in the quality of the material presented. A notable gap is the virtual absence of paediatric radiology. The passing mention of infantile conditions is worse than useless, since it may lull the unwary into a false sense of security. There is a very good list of references at the end of each chapter.

With two exceptions, all the authors are from the Department of Radiology of the University of Freiburg and the book presumably mirrors the interests of that department. These are similar to departments in this country: excellent on plain film and contrast examinations; weak on ultrasound, scintiscanning, CT scanning and paediatrics. The reviewer believes that a modern differential diagnostic text should include sizeable sections on these subjects. Within the limitations described, the book provides a good, handy differential diagnostic text.

G. M. Steiner.

Clinics in diagnostic ultrasound, Volume I, *Diagnostic ultrasound in gastro-intestinal disease.* Edited by K. J. W. Taylor, pp. ix + 177, 1979 (Churchill Livingstone, Edinburgh) £10·00.
ISBN 0–443–08046–1.

The aim of this book is to provide authoritative review articles which reflect contemporary thought in diagnostic ultrasound. The names of the editor and authors will be well-known to all with an interest in this subject.

The book consists of nine chapters, the first giving a gastroenterologist's view of the indications and value of ultrasound. This is an excellent chapter, putting into perspective the uses of ultrasound in various clinical situations. This is of increasing importance as the number of diagnostic modalities continues to proliferate. The core of the book contains chapters on diffuse and focal liver disease, the pancreas, the biliary tree and the gall bladder. The theme of the inter-relationship of various diagnostic modalities is further explored in four chapters which discuss their relationship to ultrasound. Although it is not possible to be fully comprehensive in a book of this size, the topics included have been dealt with well and in depth. with good illustrations.

The book finishes with a chapter on aspiration and biopsy procedures and nine case reports arranged to allow self-evaluation. These are a worthwhile addition.

This book will appeal to gastroenterologists as well as radiologists with an interest in ultrasound. I warmly recommend it.

K. C. Dewbury.

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Receipt of the following publications is acknowledged as a courtesy to the senders. These publications have been lodged in the library of THE BRITISH INSTITUTE OF RADIOLOGY for the use of members.

Low light and thermal imaging. IEE Conference publication No. 173. pp. xii + 69, 1979 (The Institution of Electrical Engineers, London), £7·50 (UK), £8·50 (elsewhere).
ISBN 0-85296-201-0

An International survey of distributions of histologic types of breast cancer, edited by P. Correa and W. D. Johnson. UICC Technical Report Series, vol. 35, pp. 263, 1978 (International Union against Cancer, Geneva), Sw Fr 20.
ISBN: 92-9018-035-8.

Marking of and accompanying documents for X-ray tubes and X-ray tube assemblies for medical use. IEC Publication 637, p. 23, 1979 (International Electrotechnical Commission, Geneva), Sw Fr 28.

Guidelines for the Preparation of Radiopharmaceuticals in Hospitals

Revised 1979 Edition

Special Report No. 11

A Report of a Working Party

Numerous types of diagnostic agents labelled with radio-nuclides are now in routine use for the investigation *in vivo* of human disease. Many of these radiodiagnostic agents contain radio-nuclides of short half-life and for this and other reasons it is necessary to carry out their preparation in hospitals. Little official or other guidance concerning the basic procedures required for the safe preparation of these radiopharmaceuticals has, however, been available. For this reason, following a Seminar on 'Laboratory Facilities and Working Procedures for the Hospital Preparation of Radiopharmaceuticals' held at the Royal Marsden Hospital, Sutton, in October 1974, a working party was set up to prepare some guidelines on this subject. This document comprises the report of this working party; it is concerned not with individual recipes, but with basic principles and procedures. The Report should prove helpful to many of those concerned with the preparation and use of radiopharamceuticals, and it is expected to provoke useful comment and discussion, especially on the extent to which the procedures set down conform to the requirements of the Medicines Act (1968).

In revising the present report it has not been considered necessary to revise any of the original recommendations. However, the opportunity has been taken to amend certain sections to take account of the changes in United Kingdom legislation consequent on the implementation of Article 5(a) of the European Communities Directive (Euratom, 1976) on basic safety standards for health protection against the dangers of ionizing radiation.

Additional references have also been provided, and minor changes made, where necessary to bring the text up-to-date.

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